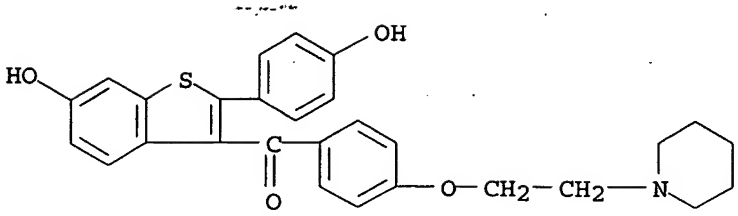


REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 10 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:635900 HCAPLUS
DOCUMENT NUMBER: 135:190841
TITLE: Method of treatment of prostate cancer and other cancers using androstenediols
INVENTOR(S): Loria, Roger M.
PATENT ASSIGNEE(S): Hollis-Eden Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001062259	A1	20010830	WO 2001-US6171	20010226
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
US 2001046980	A1	20011129	US 2001-794531	20010226
PRIORITY APPLN. INFO.:			US 2000-185115P	P 20000225

OTHER SOURCE(S): MARPAT 135:190841

AB The present invention relates to the field of cancer, and in particular hormone dependent cancers including, but not limited to prostate, breast, endometrial, ovarian, thyroid, bone, and testis. The present invention also relates to the use of steroid analogs, and in particular analogs of Δ5-androstene-3-β,17α-diol, and its epimer Δ5-androstene-3-β,17β-diol for the treatment and prevention of cancer. Drug formulations containing the analogs are exemplified as is the use of the analogs in treatment.

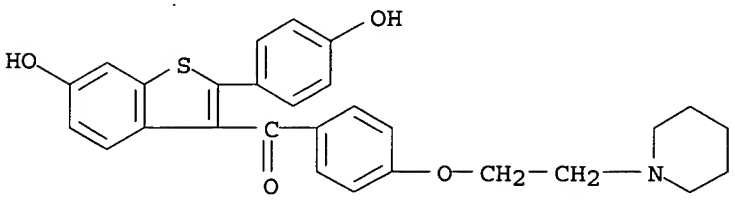
IC ICM A61K031-565
ICS A61P035-00; A61K031-565; A61K031-565
CC 2-4 (Mammalian Hormones)
Section cross-reference(s): 1, 63
IT **Androgens**
Estrogens
Hormones, animal, biological studies
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(-**dependent** cancer; method of treatment of prostate cancer and other cancers using androstenediols)

IT Mammary gland
Prostate gland
(**neoplasm**, inhibitors; method of treatment of prostate cancer and other cancers using androstenediol analogs and derivs.)

IT 50-18-0, Cyclophosphamide 51-21-8, 5-Fluorouracil 52-01-7, Spironolactone 56-53-1 59-05-2, Methotrexate 125-84-8, Aminoglutethimide 127-07-1, Hydroxyurea 427-51-0, Cyproterone acetate 566-48-3, Formestane 671-16-9, Procarbazine 3562-63-8 4342-03-4, Dacarbazine 4891-15-0, Estramustine phosphate 10540-29-1, Tamoxifen 13909-09-6, Semustine 15663-27-1, Cisplatin 18883-66-4, Streptozocin 23214-92-8, Doxorubicin 33069-62-4, Paclitaxel 52806-53-8, Hydroxyflutamide 53714-56-0, Leuprolide 65807-02-5, Goserelin 71486-22-1, Vinorelbine **84449-90-1**, Raloxifene 89778-26-7, Toremifene 90357-06-5, Bicalutamide 95058-81-4, Gemcitabine 112809-51-5, Letrozole 120511-73-1, Anastrozole 154361-50-9, Capecitabine
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(method of treatment of prostate cancer and other cancers using androstenediols in combination with other drugs)

IT **84449-90-1**, Raloxifene
RL: **BAC (Biological activity or effector, except adverse)**; BSU (Biological study, unclassified); **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(method of treatment of prostate cancer and other cancers using androstenediols in combination with other drugs)

RN 84449-90-1 HCAPLUS
CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2001:283971 HCAPLUS
DOCUMENT NUMBER: 134:300712
TITLE: Glycosides and orthoester glycosides of raloxifene and analogues and the use thereof
INVENTOR(S): Holick, Michael Francis; Ramanathan, Halasya
PATENT ASSIGNEE(S): Strakan Group PLC, UK
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

WO 2001027129	A1	20010419	WO 2000-GB3864	20001006
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
GB 2355007	A1	20010411	GB 1999-28100	19991126
PRIORITY APPLN. INFO.:			US 1999-158141P P	19991008
			US 2000-231573P P	20000911

OTHER SOURCE(S): MARPAT 134:300772

AB Raloxifene and raloxifene analog glycosides and orthoester glycosides afford greater serum bioavailability of the hydroxylated parent compound, and are useful for treating or preventing a number of conditions that may be treated with an anti-estrogenic or an anti-androgenic compound To a mixture of 0.5 g raloxifene and 1.6 g silver silicate in dry acetonitrile was added 3 g mol. sieves and stirred for 20 min. To the above suspension was added 1.0 g acetobromo-α-D-glucose and heated for 2 h at 60°, then filtered through a bed of silica gel and eluted with dichloromethane and methanol. The yellow eluent was concentrated under vacuum to obtain yellowish crystals. Proton NMR spectrum showed the crystals were consisted of 2 possible monoglucosides and a doubly glycosylated product.

IC ICM C07H015-26
ICS A61K031-70; A61P035-00; A61P019-10; A61P025-00; A61P025-28

CC 63-5 (Pharmaceuticals)
Section cross-reference(s): 27

IT **Androgens**
Estrogens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cancer **dependent**-; glycosides and orthoester glycosides of raloxifene and analogs and use thereof)

IT Mammary gland
Prostate gland
(**neoplasm**, inhibitors; glycosides and orthoester glycosides of raloxifene and analogs and use thereof)

IT **334758-15-5P 334758-16-6P 334758-17-7P**
334758-18-8P 334758-19-9P 334758-20-2P
RL: RCT (Reactant); SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(glycosides and orthoester glycosides of raloxifene and analogs and use thereof)

IT **84449-90-1**, Raloxifene
RL: RCT (Reactant); **THU (Therapeutic use)**; BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(glycosides and orthoester glycosides of raloxifene and analogs and use thereof)

IT **84449-90-1DP**, Raloxifene, glycosides and orthoester
RL: SPN (Synthetic preparation); **THU (Therapeutic use)**; BIOL (Biological study); PREP (Preparation); USES (Uses)
(glycosides and orthoester glycosides of raloxifene and analogs and use thereof)

IT **334758-15-5P 334758-16-6P 334758-17-7P**
334758-18-8P 334758-19-9P 334758-20-2P
RL: RCT (Reactant); SPN (Synthetic preparation); **THU (Therapeutic**

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=> d que
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                 OR PROSTATE CANCER
L22               STR
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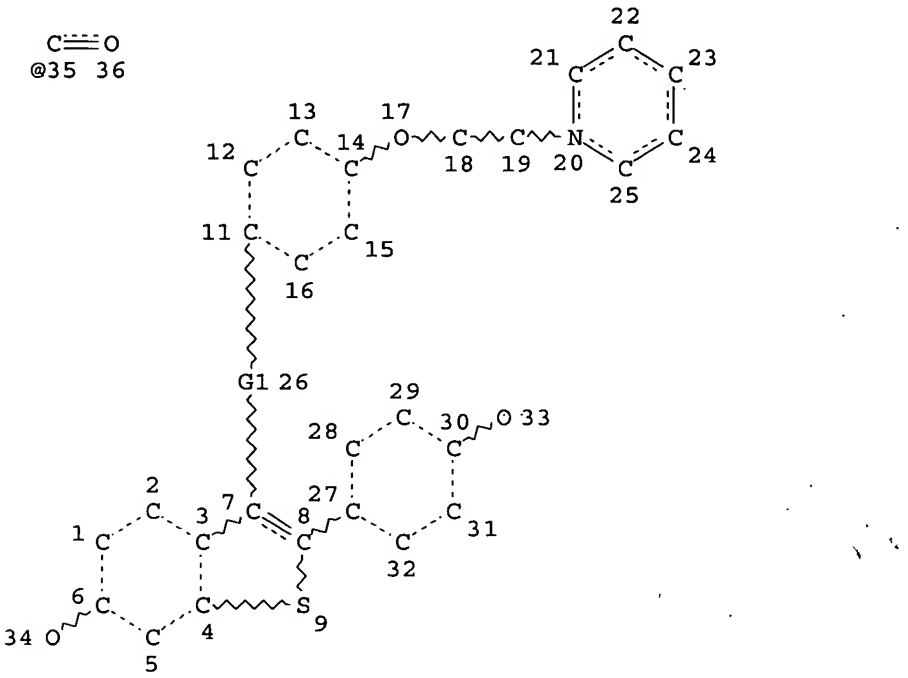

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VAR G1=O/35
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  35

STEREO ATTRIBUTES: NONE
L24          359 SEA FILE=REGISTRY SSS FUL L22
L34          320 SEA FILE=CANCERLIT ABB=ON  PLU=ON  L24
L37            8 SEA FILE=CANCERLIT ABB=ON  PLU=ON  L34 AND L13
L38           11 SEA FILE=CANCERLIT ABB=ON  PLU=ON  "LY 353381"+PFT/CN
L39           13 SEA FILE=CANCERLIT ABB=ON  PLU=ON  L38 OR ARZOXIFENE
L40          409 SEA FILE=CANCERLIT ABB=ON  PLU=ON  RALOXIFENE/CN OR RALOXIFENE?

L41            1 SEA FILE=CANCERLIT ABB=ON  PLU=ON  L39 AND L13
L42           11 SEA FILE=CANCERLIT ABB=ON  PLU=ON  L40 AND L13
L44           12 SEA FILE=CANCERLIT ABB=ON  PLU=ON  L37 OR L41 OR L42


=> d l44 bib ab hitind 1-12

L44  ANSWER 1 OF 12  CANCERLIT on STN
AN   2002195881     CANCERLIT
DN   22194351   PubMed ID: 12084714
TI   Raloxifene, a mixed estrogen agonist/antagonist, induces
```

apoptosis through cleavage of BAD in TSU-PR1 human cancer cells.

AU Kim Heung Tae; Kim Byung Chul; Kim Isaac Yi; Mamura Mizuko; Seong Do Hwan; Jang Ja-June; Kim Seong-Jin
CS Laboratory of Cell Regulation and Carcinogenesis, NCI, National Institutes of Health, Bethesda, Maryland 20892, USA.

SO JOURNAL OF BIOLOGICAL CHEMISTRY, (2002 Sep 6) 277 (36) 32510-5.
Journal code: 2985121R. ISSN: 0021-9258.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2002448063
EM 200210
ED Entered STN: 20021115
Last Updated on STN: 20021115

AB Selective estrogen receptor modulator is a proven agent for chemoprevention and chemotherapy of cancer. **Raloxifene**, a mixed estrogen agonist/antagonist, was developed to prevent osteoporosis and potentially reduce the risk of breast cancer. In this study, we examined the effect of **raloxifene** on the TSU-PR1 cell line. This cell line was originally reported to be a **prostate cancer** cell line, but recently it has been shown to be a human bladder transitional cell carcinoma cell line. The TSU-PR1 cell line contains high levels of estrogen receptor beta. Following treatment with **raloxifene**, evidence of apoptosis, including change in nuclear morphology, DNA fragmentation, and cytochrome c release, was observed in a dose-dependent manner in the TSU-PR1 cells (10(-9) to 10(-6) m range). We observed no detectable change in the steady-state levels of Bax, Bcl-2, and Bcl-X(L) following **raloxifene** treatment. However, **raloxifene** induced caspase-dependent cleavage of BAD to generate a 15-kDa truncated protein. Overexpression of a double mutant BAD resistant to caspase 3 cleavage blocked **raloxifene**-induced apoptosis. These results demonstrate that **raloxifene** induces apoptosis through the cleavage of BAD in TSU-PR1 cells. This molecular mechanism of apoptosis suggests that **raloxifene** may be a therapeutic agent for human bladder cancer.

CT Check Tags: Human
Amino Acid Chloromethyl Ketones: PD, pharmacology
*Antineoplastic Agents: PD, pharmacology
*Apoptosis
*Bladder Neoplasms: ME, metabolism
Bladder Neoplasms: PA, pathology
*Carrier Proteins: ME, metabolism
Caspases: ME, metabolism
Cell Division
Cell Membrane: ME, metabolism
Cell Nucleus: PA, pathology
Cycloheximide: PD, pharmacology
Cytochrome c: ME, metabolism
DNA Fragmentation
Dose-Response Relationship, Drug
*Estrogen Receptor Modulators: PD, pharmacology
In Situ Nick-End Labeling
Membrane Potentials
Mitochondria: ME, metabolism
Phosphorylation
Protein Binding
Protein Synthesis Inhibitors: PD, pharmacology
Proto-Oncogene Proteins c-bcl-2: ME, metabolism

***Raloxifene: PD, pharmacology**
Retroviridae: ME, metabolism
Time Factors
Tumor Cells, Cultured
RN 66-81-9 (Cycloheximide); **84449-90-1 (Raloxifene)**; 9007-43-6 (Cytochrome c)
CN 0 (Amino Acid Chloromethyl Ketones); 0 (Antineoplastic Agents); 0 (Bad protein); 0 (Carrier Proteins); 0 (Estrogen Receptor Modulators); 0 (Protein Synthesis Inhibitors); 0 (Proto-Oncogene Proteins c-bcl-2); 0 (bcl-x protein); 0 (benzyloxycarbonylvalyl-alanyl-aspartyl fluoromethyl ketone); EC 3.4.22.- (CPP32 protein); EC 3.4.22.- (Caspases)

L44 ANSWER 2 OF 12 CANCERLIT on STN
AN 2002190615 CANCERLIT
DN 22219976 PubMed ID: 12235008
TI **Raloxifene**, a mixed estrogen agonist/antagonist, induces apoptosis in androgen-independent human **prostate cancer** cell lines.
AU Kim Isaac Yi; Kim Byung-Chul; Seong Do Hwan; Lee Dug Keun; Seo Jeong-Meen; Hong Young Jin; Kim Heung-Tae; Morton Ronald A; Kim Seong-Jin
CS Laboratory of Cell Regulation and Carcinogenesis, National Cancer Institute/NIH, Building 41, Room C629, 9000 Rockville Pike, Bethesda, MD 20892, USA.
SO CANCER RESEARCH, (2002 Sep 15) 62 (18) 5365-9.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2002472917
EM 200210
ED Entered STN: 20021115
Last Updated on STN: 20021115
AB **Raloxifene**, a selective estrogen receptor (ER) modulator, is a mixed estrogen agonist/antagonist that has been shown to prevent osteoporosis and breast cancer in women. Because the prostate contains high levels of ER-beta, the present study investigated the effect of **raloxifene** in three well-characterized, androgen-independent human **prostate cancer** cell lines: (a) PC3; (b) PC3M; and (c) DU145. Reverse transcriptase-PCR and Western blot analysis for ER-alpha and ER-beta demonstrated that all three cell lines express ER-beta, whereas only PC3 and PC3M cells were positive for ER-alpha. After the treatment with **raloxifene**, a dramatic increase in cell death was observed in a dose-dependent manner in the three **prostate cancer** cell lines (10(-9) to 10(-6) M range). Because the three **prostate cancer** cell lines demonstrated similar morphological changes after the **raloxifene** treatment, PC3 (ER-alpha/ER-beta+) and DU145 (ER-beta+ only) cells were selected to further characterize the **raloxifene**-induced cell death. Using the nucleus-specific stain 4',6-diamidino-2-phenylindole, nuclear fragmentation was observed in a time-dependent manner in both cell lines after exposure to 10(-6) M **raloxifene**. Using the terminal deoxynucleotidyl transferase-mediated nick end labeling apoptotic assay, it was demonstrated that the nuclear fragmentation was caused by apoptosis. To investigate the possibility that caspase activation is involved in **raloxifene**-induced apoptosis, cells were treated with the pan-caspase inhibitor ZVAD. The results demonstrated that the dramatic change in cellular morphology after treatment with **raloxifene** was no longer observed when cells were pretreated with

ZVAD. Immunoblot demonstrated activation of caspases 8 and 9 in PC3 and DU145 cells, respectively. Taken together, these results demonstrate that the mixed estrogen agonist/antagonist, **raloxifene**, induces apoptosis in androgen-independent human **prostate cancer** cell lines.

CT Check Tags: Human; Male; Support, U.S. Gov't, P.H.S.
*Apoptosis: DE, drug effects
Neoplasms, Hormone-Dependent: DT, drug therapy
Neoplasms, Hormone-Dependent: PA, pathology
***Prostatic Neoplasms: DT, drug therapy**
Prostatic Neoplasms: PA, pathology
***Raloxifene: PD, pharmacology**
*Selective Estrogen Receptor Modulators: PD, pharmacology
Tumor Cells, Cultured

RN **84449-90-1 (Raloxifene)**
CN 0 (Selective Estrogen Receptor Modulators)

L44 ANSWER 3 OF 12 CANCERLIT on STN
AN 2002169483 CANCERLIT
DN 22091919 PubMed ID: 12097269
TI **Raloxifene**, a selective estrogen receptor modulator, induces apoptosis in androgen-responsive human **prostate cancer** cell line LNCaP through an androgen-independent pathway.
AU Kim Isaac Yi; Seong Do Hwan; Kim Byung-Chul; Lee Dug Keun; Remaley Alan T; Leach Fredrick; Morton Ronald A; Kim Seong-Jin
CS Laboratory of Cell Regulation and Carcinogenesis, National Cancer Institute, Bethesda, Maryland 20892, USA.
SO CANCER RESEARCH, (2002 Jul 1) 62 (13) 3649-53.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2002353962
EM 200208
ED Entered STN: 20021018
Last Updated on STN: 20021018
AB **Raloxifene**, a selective estrogen receptor (ER) modulator, is a mixed estrogen agonist/antagonist that has been shown to prevent osteoporosis and breast cancer in women. Because the prostate contains a high level of ER-beta, the present study investigated the effect of **raloxifene** in the androgen-sensitive human **prostate cancer** cell line LNCaP. Previously, it has been demonstrated that LNCaP cells express ER-beta but not ER-alpha and that tamoxifene induces apoptosis in these cells. After treatment with **raloxifene**, a dramatic increase in cell death occurred in a dose-dependent manner (10(-9) to 10(-6) M range). Using the terminal deoxynucleotidyl transferase-mediated nick end labeling apoptotic assay, we demonstrated that the nuclear fragmentation was due to apoptosis. The dramatic change in cellular morphology after treatment with **raloxifene** was no longer observed when cells were pretreated with a pan-caspase inhibitor, Z-VAD-FMK, and a specific caspase-9 inhibitor, Z-LEHD-FMK. Furthermore, immunoblot demonstrated an activation of caspase-9 in LNCaP cells. Because LNCaP cells contain a mutated androgen receptor that allows cellular proliferation in the presence of antiandrogens, prostate-specific antigen assay and transfection with a reporter construct containing luciferase gene under the control of androgen response element (pARE) were carried out. The results demonstrated that **raloxifene** does not significantly alter androgen receptor activity in LNCaP cells. Taken

together, these results demonstrate that **raloxifene**, a selective ER modulator, induces apoptosis in the androgen-sensitive human **prostate cancer** cell line LNCaP through an androgen-independent pathway.

CT Check Tags: Human; Male
*Androgens: PH, physiology
*Apoptosis: DE, drug effects
Apoptosis: PH, physiology
Dose-Response Relationship, Drug
Neoplasms, Hormone-Dependent: DT, drug therapy
*Neoplasms, Hormone-Dependent: PA, pathology
Prostatic Neoplasms: DT, drug therapy
***Prostatic Neoplasms: PA, pathology**
***Raloxifene: PD, pharmacology**
Receptors, Androgen: PH, physiology
*Selective Estrogen Receptor Modulators: PD, pharmacology
Tumor Cells, Cultured

RN **84449-90-1 (Raloxifene)**

CN 0 (Androgens); 0 (Receptors, Androgen); 0 (Selective Estrogen Receptor Modulators)

L44 ANSWER 4 OF 12 CANCERLIT on STN
AN 2002133265 CANCERLIT
DN 21936219 PubMed ID: 11937434
TI Complementary therapies for reducing the risk of osteoporosis in patients receiving luteinizing hormone-releasing hormone treatment/orchiectomy for **prostate cancer**: a review and assessment of the need for more research.
AU Moyad Mark A
CS Department of Urology, University of Michigan Medical Center, Ann Arbor, Michigan, USA.
SO UROLOGY, (2002 Apr) 59 (4 Suppl 1) 34-40. Ref: 58
Journal code: 0366151. ISSN: 1527-9995.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2002205259
EM 200204
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB Osteoporosis in women has received a substantial amount of attention, but its impact in men is also significant and noteworthy. Those men who benefit from treatment for **prostate cancer** with androgen deprivation therapy (ADT) may also be at a higher risk for osteoporosis. Pharmacologic approaches to reduce this risk have received some attention. For example, agents such as bisphosphonates, estrogen receptor-binding drugs (diethylstilbestrol, tamoxifen, and **raloxifene**), calcitonin, and fluoride are some of the more promising interventions that have been previously outlined. In addition, statin drugs, or hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, have recently been hypothesized to lower osteoporosis risk. However, complementary therapies, which may also have an impact on reducing osteoporosis risk, have not received attention. Dietary and supplemental calcium and vitamin D have been shown, in some preliminary investigations, to maintain bone density in women and men. Numerous healthy and affordable dietary sources of this mineral and vitamin exist,

and large intakes can be realistically achieved through proper education. Similarly, the supplemental dosages required to impact risk have been moderate, appear to be safe, are of low cost, and thus may provide an additional route for reducing risk, especially if these interventions are initiated at the start of medical treatment. More studies in men receiving ADT are needed because the existing work has mostly focused on men without castrate levels of male hormone. Additionally, many studies with conventional and nonconventional agents have only focused on individuals with baseline osteoporosis, rather than normal bone mineral densities or osteopenia. Other promising complementary therapies, such as weight-bearing exercise and abstaining from smoking, may also be of benefit. Newer estrogenic-type supplements (eg, ipriflavone) appear interesting and have some preliminary data, but more research is desperately required to determine their actual impact and potential for adverse effects (such as lymphocytopenia from a recent trial). Simple, inexpensive, and potentially effective dietary and supplemental approaches to reduce the risk of osteoporosis in men exist, and they should be discussed with patients. Whether these approaches effectively reduce the risk of osteoporosis in men receiving androgen ablation remains to be determined. The possibility is intriguing, and future research is needed. In the meantime, it is important to keep in mind that these complementary approaches are, at the very least, an integral part of the conventional options used today to the reduce the risk of osteoporosis in men and women.

CT Check Tags: Female; Human; Male
Aged
Aged, 80 and over
*Calcium: AD, administration & dosage
Complementary Therapies
*Dietary Supplements
Gonadorelin: AE, adverse effects
Gonadorelin: TU, therapeutic use
Isoflavones: AD, administration & dosage
Life Style
Middle Age
Orchiectomy: AE, adverse effects
Osteoporosis: ET, etiology
*Osteoporosis: PC, prevention & control
***Prostatic Neoplasms: CO, complications**
Prostatic Neoplasms: DT, drug therapy
Risk
*Vitamin D: AD, administration & dosage

RN 1406-16-2 (Vitamin D); 33515-09-2 (Gonadorelin); 35212-22-7 (ipriflavone); 7440-70-2 (Calcium)

CN 0 (Isoflavones)

L44 ANSWER 5 OF 12 CANCERLIT on STN

AN 2002070526 CANCERLIT

DN 21379721 PubMed ID: 11486708

TI Selective estrogen receptor modulation: the search for an ideal hormonal therapy for breast cancer.

AU Dhingra K

CS Hoffmann-La Roche, Inc., Nutley, New Jersey 07110, USA.. kapil.dhingra@Roche.com

SO CANCER INVESTIGATION, (2001) 19 (6) 649-59. Ref: 67
Journal code: 8307154. ISSN: 0735-7907.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)

(REVIEW, ACADEMIC)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2001441220
EM 200108
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB Female hormones, especially estrogens, play an important role in the pathogenesis of breast neoplasms and are a principal determinant of their biological behavior. Endocrine manipulation through medical or surgical means can often lead to objective shrinkage of breast tumors. Tamoxifen, a triphenylethylene estrogen receptor modulator, is currently the most widely used hormonal treatment for breast cancer. It has been conclusively demonstrated to reduce the risk of relapse following definitive local therapy (and systemic chemotherapy, when indicated) of invasive or noninvasive breast cancer. Recently, it has also been shown to reduce the incidence of breast cancer in healthy women who are at high risk of developing the disease. In addition, it can prevent osteoporosis and reduce the risk of fractures in postmenopausal women. However, its use is also complicated by an increased incidence of endometrial hyperplasia/carcinoma, venous thromboembolism, cataracts, and in some cases, emergence of tamoxifen-dependent clones of breast cancer. These side effects (except cataracts) are believed to be related to estrogen-agonist effects of tamoxifen. Newer drugs, which are "pure antiestrogens" or inhibitors of estrogen biosynthesis, are devoid of such estrogen-agonist activity and may not have the liability of many of these side effects. However, these agents would also be expected to lack the potentially beneficial effects of tamoxifen on lipids and skeletal system. The ability of tamoxifen to act as an estrogen-agonist or estrogen-antagonist in a tissue-specific fashion has led to the concept of selective estrogen-receptor modulation. Selective estrogen receptor modulators (SERMs), which are devoid of estrogen-agonist effects on the uterus or breast cancer cells but retain potentially beneficial effects on bones and lipids, have been described as "ideal" SERMs. A number of such compounds are currently being tested. **Raloxifene** is already approved for prevention of osteoporosis and has potential efficacy for prevention and treatment of breast cancer. An analogue of **raloxifene**, LY353381, is currently in Phase II clinical trials for treatment of breast cancer, with promising early results. EM800 and CP336156 are other promising ideal SERMs in clinical trials. These compounds may provide better treatment and chemoprevention alternatives for breast cancer as compared to tamoxifen, aromatase inhibitors, and pure antiestrogens. In addition, they may also prove to be useful for the treatment and prevention of **prostate cancer** as well as for treating benign gynecological diseases such as fibroids and endometriosis. Future laboratory efforts should focus on further broadening the efficacy profile of SERMs (e.g., prevention of Alzheimer's disease and elevation of high-density lipoproteins to improve the likelihood of cardiovascular benefit) and narrowing their side-effect profile (e.g., risk of thromboembolism and hot flashes).
CT Check Tags: Female; Human
Antineoplastic Agents, Hormonal: AE, adverse effects
*Antineoplastic Agents, Hormonal: TU, therapeutic use
*Breast Neoplasms: DT, drug therapy
Drug Design
Estrogen Receptor Modulators: AE, adverse effects
*Estrogen Receptor Modulators: TU, therapeutic use
Raloxifene: TU, therapeutic use
*Receptors, Estrogen: DE, drug effects

Receptors, Estrogen: PH, physiology
Tamoxifen: AE, adverse effects
Tamoxifen: TU, therapeutic use
RN 10540-29-1 (Tamoxifen); **84449-90-1 (Raloxifene)**
CN 0 (Antineoplastic Agents, Hormonal); 0 (Estrogen Receptor Modulators); 0 (Receptors, Estrogen)

L44 ANSWER 6 OF 12 CANCERLIT on STN
AN 2002046567 CANCERLIT
DN 21193270 PubMed ID: 11295598
TI Selective estrogen receptor modulators for the chemoprevention of **prostate cancer**.
AU Steiner M S; Raghow S; Neubauer B L
CS Department of Urology, University of Tennessee, Memphis, Tennessee 38104, USA.. MSteiner@utmem.edu
SO UROLOGY, (2001 Apr) 57 (4 Suppl 1) 68-72.
Journal code: 0366151. ISSN: 1527-9995.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2001265933
EM 200106
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB The ability to interfere with prostate carcinogenesis, and as a consequence, prevent **prostate cancer** with drugs is the basis for chemoprevention. The prostate contains estrogen receptors in both the stroma and epithelium. Both animal models and human epidemiologic studies have implicated estrogens as an initiator of **prostate cancer**. In the aging male, **prostate cancer** occurs in an environment of rising estrogen and decreasing androgen levels. Selective estrogen receptor modulators (SERMs) have shown the ability to prevent (GTx-006 [acapodene]) and treat (GTx-006 and **arzoxifene**) **prostate cancer**, suggesting that they may be used in **prostate cancer** chemoprevention. A phase 2 clinical trial using GTx-006 for **prostate cancer** chemoprevention is currently being conducted.
CT Check Tags: Human; Male
Age Factors
Androgens: BL, blood
*Anticarcinogenic Agents: TU, therapeutic use
Estrogen Antagonists: PD, pharmacology
Estrogen Receptor Modulators: TU, therapeutic use
Estrogens: BL, blood
Estrogens, Non-Steroidal: PD, pharmacology
Piperidines: PD, pharmacology
Prostate: GD, growth & development
Prostatic Neoplasms: ET, etiology
***Prostatic Neoplasms: PC, prevention & control**
Receptors, Estrogen: PH, physiology
*Selective Estrogen Receptor Modulators: TU, therapeutic use
Tamoxifen: PD, pharmacology
Thiophenes: PD, pharmacology
RN 10540-29-1 (Tamoxifen)
CN 0 (Androgens); 0 (Anticarcinogenic Agents); 0 (Estrogen Antagonists); 0 (Estrogen Receptor Modulators); 0 (Estrogens); 0 (Estrogens, Non-Steroidal); **0 (LY 353381)**; 0 (Piperidines); 0 (Receptors, Estrogen); 0 (Selective Estrogen Receptor Modulators); 0 (Thiophenes); 0

(phytoestrogens)

L44 ANSWER 7 OF 12 CANCERLIT on STN
AN 2000227625 CANCERLIT
DN 20227625 PubMed ID: 10762741
TI Recent advances in cancer chemoprevention, with emphasis on breast and colorectal cancer.
AU Decensi A; Costa A
CS Chemoprevention Unit, European Institute of Oncology, via Ripamonti 435, 20141, Milan, Italy.. andrea.adecensi@ieo.it
SO EUROPEAN JOURNAL OF CANCER, (2000 Apr) 36 (6) 694-709. Ref: 86
Journal code: 9005373. ISSN: 0959-8049.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2000227625
EM 200006
ED Entered STN: 20000719
Last Updated on STN: 20000719
AB Chemoprevention is a recently introduced and rapidly growing area of oncology that is identifying agents with a potentially preventive role in cancer. Several clinical trials have recently shown the feasibility of this approach in reducing the risk of major human cancers. In the USA, a large trial that demonstrated a reduction of approximately 50% in the risk of developing breast cancer led to Food and Drug Administration (FDA) approval of tamoxifen as a preventive agent in women at increased risk. Although the results could not be reproduced in two smaller European trials, further investigations into this agent are clearly warranted. **Raloxifene**, another selective oestrogen receptor modulator which has reduced the risk of breast cancer in a trial in women with osteoporosis, is being compared with tamoxifen in a large primary prevention trial in at-risk women. Retinoids are a group of compounds that have proved especially effective in reducing the occurrence of second primary tumours in subjects with skin, head and neck or liver cancer. Fenretinide, a synthetic retinoic acid derivative, has recently been shown to decrease the occurrence of a second breast malignancy in premenopausal women. Results with non-steroidal anti-inflammatory drugs (NSAIDs) have proved consistently encouraging in epidemiological studies in lowering the incidence of colorectal cancer. Clinical trials with selective cyclo-oxygenase inhibitors potentially devoid of gastrointestinal (GI) toxicity are currently underway in at-risk subjects. Calcium and selenium have also received much attention as chemopreventive agents. Originally investigated against skin cancer, selenium showed efficacy in reducing prostate, lung and colon cancer incidence. Similarly, vitamin E was effective in reducing **prostate cancer** incidence and mortality in a lung cancer prevention trial in heavy smokers. The challenges of conducting well-designed and unequivocal chemoprevention trials are considerable, but advances in techniques of identification of at-risk subjects and establishing surrogate endpoint biomarkers should contribute greatly to future studies. Current knowledge suggests that a pharmacological approach to preventing cancer, using natural or synthetic agents, could become an important way forward.
CT Check Tags: Female; Human
Antineoplastic Agents: TU, therapeutic use
Breast Neoplasms: BL, blood
Breast Neoplasms: PA, pathology

*Breast Neoplasms: PC, prevention & control
*Chemoprevention: MT, methods
Colorectal Neoplasms: BL, blood
Colorectal Neoplasms: PA, pathology
*Colorectal Neoplasms: PC, prevention & control
Insulin-Like Growth Factor I: AN, analysis
Mammography
Tumor Markers, Biological: AN, analysis
RN 67763-96-6 (Insulin-Like Growth Factor I)
CN 0 (Antineoplastic Agents); 0 (Tumor Markers, Biological)

L44 ANSWER 8 OF 12 CANCERLIT on STN
AN 96625501 CANCERLIT
DN 96625501
TI Drugs that block steroid hormone action for the treatment of breast and **prostate cancer**.
AU Kendrick-Parker C J; Jordan V C
CS Dept. of Human Oncology and Pharmacology, Univ. of Wisconsin, Madison, WI 53792.
SO Non-serial, (1995) Cancer Chemotherapeutic Agents. WO Foye, ed. (Professional Reference Book) American Chemical Society, Washington, DC, p. 389-428, 1995. .
DT Book; (MONOGRAPH)
LA English
FS Institute for Cell and Developmental Biology
EM 199606
ED Entered STN: 19970509
Last Updated on STN: 19970509
AB Steroid hormones are considered to be major determinants of the development of breast, prostate and uterine cancers. It is only natural that development and application of specific antihormones has occurred to treat these cancers. The focus of this chapter is on antihormones in breast and **prostate cancers**. In the first section on the topic of breast cancer, there is discussion of the mechanism of action of antiestrogens, followed by consideration of specific agents: tamoxifen; droloxifene; toremifene; trioxifene; **raloxifene**; zindoxifene; and the pure steroidal antiestrogens, ICI 164,384 and ICI 182,780. Inhibition of steroid biosynthesis, particularly by the use of aromatase inhibitors, is another approach that has been used for treating breast cancer. The mechanism of action of this class of agents is discussed with respect to aminoglutethimide, testolactone, pyridoglutethimide, CGS 20,267, and the triazole derivatives R76713 and R83842 (Vorazole). Specific discussion of the use of aminoglutethimide, formestane, and fadrazole (CGS 16949A) follows. Turning to **prostate cancer**, the mechanism of action and use of the nonsteroidal antiandrogens, flutamide, Casodex, and anandron are discussed first, followed by the inhibitors of steroid biosynthesis, finasteride and ketoconazole. The final section is a discussion of future potential. (314 Refs)
CN EC 1.14.13.- (Aromatase); 0 (Androgen Antagonists); 0 (Estrogen Antagonists)

L44 ANSWER 9 OF 12 CANCERLIT on STN
AN 96347982 CANCERLIT
DN 96347982 PubMed ID: 8757185
TI **Raloxifene**, retinoids, and lavender: "me too" tamoxifen alternatives under study.
AU Ziegler J
SO JOURNAL OF THE NATIONAL CANCER INSTITUTE, (1996 Aug 21) 88 (16) 1100-2.

Journal code: 7503089. ISSN: 0027-8874.
CY United States
DT News Announcement
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 96347982
EM 199609
ED Entered STN: 19961008
Last Updated on STN: 19961008
CT Check Tags: Female; Human; Male
Antineoplastic Agents, Hormonal: AE, adverse effects
*Antineoplastic Agents, Hormonal: TU, therapeutic use
Breast Neoplasms: DT, drug therapy
Clinical Trials
Drugs, Investigational: TU, therapeutic use
Estrogen Antagonists: AE, adverse effects
*Estrogen Antagonists: TU, therapeutic use
*Neoplasms: DT, drug therapy
Oils, Volatile: AE, adverse effects
*Oils, Volatile: TU, therapeutic use
Ovarian Neoplasms: DT, drug therapy
Piperidines: AE, adverse effects
*Piperidines: TU, therapeutic use
*Plants, Medicinal
Prostatic Neoplasms: DT, drug therapy
Raloxifene
Retinoids: AE, adverse effects
*Retinoids: TU, therapeutic use
Tamoxifen: AA, analogs & derivatives
Tamoxifen: TU, therapeutic use
Toremifene: TU, therapeutic use
RN 10540-29-1 (Tamoxifen); 116057-75-1 (pyrrolidino-4-iodotamoxifen); 8000-28-0 (lavender oil); 82413-20-5 (3-hydroxytamoxifen); **84449-90-1 (Raloxifene)**; 89778-26-7 (Toremifene)
CN 0 (Antineoplastic Agents, Hormonal); 0 (Drugs, Investigational); 0 (Estrogen Antagonists); 0 (Oils, Volatile); 0 (Piperidines); 0 (Retinoids)

L44 ANSWER 10 OF 12 CANCERLIT on STN
AN 96043753 CANCERLIT
DN 96043753 PubMed ID: 7479389
TI **Raloxifene** (LY156758) produces antimetastatic responses and extends survival in the PAIII rat prostatic adenocarcinoma model.
AU Neubauer B L; Best K L; Counts D F; Goode R L; Hoover D M; Jones C D; Sarosdy M F; Shaar C J; Tanzer L R; Merriman R L
CS Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis 46285, USA.
SO PROSTATE, (1995 Oct) 27 (4) 220-9.
Journal code: 8101368. ISSN: 0270-4137.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 96043753
EM 199512
ED Entered STN: 19960126
Last Updated on STN: 19960126
AB The benzothiophene antiestrogen, **raloxifene** (LY156758), has selective estrogen pharmacological antagonist activity in rats. The PAIII rat prostatic adenocarcinoma model was used to evaluate the effects of

this agent on the lymphatic and pulmonary metastasis and survival in tumor-bearing male Lobund-Wistar (LW) rats. **Raloxifene** was inactive against colony formation of PAIII cells in vitro. Similarly, following subcutaneous (s.c.) implantation of 10(6) PAIII cells in the tail, s.c. administration of **raloxifene** (2.0, 10.0, or 20.0 mg/kg/day) for 30 days failed to demonstrate cytoreductive activity against primary tumor growth in the tail. However, in these same animals, **raloxifene** administration produced significant ($P < 0.05$) inhibition of PAIII metastasis from the primary tumor in the tail to the gluteal and iliac lymph nodes (maximal responses = 89% and 81% from control values, respectively). PAIII metastasis to the lungs was significantly inhibited by **raloxifene** treatment. Numbers of pulmonary foci in PAIII-bearing rats were significantly ($P < 0.05$) reduced by **raloxifene** administration in a dose-related manner (maximal reduction = 97% from control values). In these animals, maximal regression of 20% for ventral prostate and 21% for seminal vesicle were also seen after **raloxifene** administration ($P < 0.05$ for both). Coadministration of E2B and **raloxifene** had no consistent antagonistic effect upon the antitumor responses produced by **raloxifene**. **Raloxifene** (40.0 mg/kg/day for 28 days) produced marked decreases in PAIII metastasis in the lymphatic and pulmonary components. Continued administration of the compound produced significant ($P < 0.05$) extension of survival of PAIII-bearing rats. Further studies are needed to define the maximal antitumor efficacy and the mechanism of action of **raloxifene** in urogenital solid tumor animal models. These data support the contention that **raloxifene** represents a class of active antimetastatic agents with potential efficacy in the treatment of hormone-insensitive human prostatic cancer.

CT Check Tags: Animal; Male
Adenocarcinoma: DT, drug therapy
Adenocarcinoma: MO, mortality
*Adenocarcinoma: PA, pathology
Adrenal Glands: DE, drug effects
Adrenal Glands: PA, pathology
Antimetabolites, Antineoplastic: PD, pharmacology
Antimetabolites, Antineoplastic: TU, therapeutic use
*Antineoplastic Agents: PD, pharmacology
Antineoplastic Agents: TU, therapeutic use
Disease Models, Animal
Dose-Response Relationship, Drug
Estradiol: PD, pharmacology
Estradiol: TU, therapeutic use
*Estrogen Antagonists: PD, pharmacology
Estrogen Antagonists: TU, therapeutic use
Fluorouracil: PD, pharmacology
Fluorouracil: TU, therapeutic use
Incidence
Lung Neoplasms: EP, epidemiology
Lung Neoplasms: PC, prevention & control
Lung Neoplasms: SC, secondary
Lymphatic Metastasis
Organ Weight: DE, drug effects
*Piperidines: PD, pharmacology
Piperidines: TU, therapeutic use
Prostate: DE, drug effects
Prostate: PA, pathology
Prostatic Neoplasms: DT, drug therapy
Prostatic Neoplasms: MO, mortality
***Prostatic Neoplasms: PA, pathology**

Raloxifene
Random Allocation
Rats
Rats, Wistar
Survival Rate
Testis: DE, drug effects
Testis: PA, pathology
Weight Gain: DE, drug effects
RN 50-28-2 (Estradiol); 51-21-8 (Fluorouracil); **84449-90-1 (Raloxifene)**
CN 0 (Antimetabolites, Antineoplastic); 0 (Antineoplastic Agents); 0 (Estrogen Antagonists); 0 (Piperidines)

L44 ANSWER 11 OF 12 CANCERLIT on STN
AN 92005429 CANCERLIT
DN 92005429 PubMed ID: 1913642
TI Characteristics of the biphasic action of androgens and of the potent antiproliferative effects of the new pure antiestrogen EM-139 on cell cycle kinetic parameters in LNCaP human prostatic cancer cells.
AU de Launoit Y; Veilleux R; Dufour M; Simard J; Labrie F
CS Medical Research Council of Canada Group in Molecular Endocrinology, CHUL Research Center, Quebec.
SO CANCER RESEARCH, (1991 Oct 1) 51 (19) 5165-70.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 92005429
EM 199110
ED Entered STN: 19941107
Last Updated on STN: 19970509
AB The most potent steroid in human prostatic carcinoma LNCaP cells, i.e., dihydrotestosterone (DHT), has a biphasic stimulatory effect on cell proliferation. At the maximal stimulatory concentration of 0.1 nM DHT, analysis of cell kinetic parameters shows a decrease of the G0-G1 fraction with a corresponding increase of the S and G2 + M fractions. In contrast, concentrations of 1 nM DHT or higher induce a return of cell proliferation to control levels, reflected by an increase in the G0-G1 fraction at the expense of the S and especially the G2 + M fractions. Continuous labeling for 144 h with the nucleotide analogue 5'-bromodeoxyuridine shows that the percentage of cycling LNCaP cells rises more than 90% after treatment with stimulatory concentrations of DHT, whereas in control cells as well as in cells treated with high concentrations of the androgen, this value remains below 50%. Although LNCaP cells do not contain detectable estrogen receptors, the new pure steroidal antiestrogen EM-139 not only reversed the stimulation of cell proliferation and cell kinetics induced by stimulatory doses of DHT but also inhibited basal cell proliferation.
CT Check Tags: Human; In Vitro; Male; Support, Non-U.S. Gov't
*Androgens: PD, pharmacology
Androstane-3,17-diol: PD, pharmacology
Binding, Competitive
*Cell Cycle: DE, drug effects
Dose-Response Relationship, Drug
Drug Antagonism
*Estradiol: AA, analogs & derivatives
Estradiol: PD, pharmacology
*Estrogen Antagonists: PD, pharmacology
Estrone: PD, pharmacology

Flow Cytometry
Flutamide: AA, analogs & derivatives
Flutamide: PD, pharmacology
Metribolone: ME, metabolism
Piperidines: PD, pharmacology
***Prostatic Neoplasms: DT, drug therapy**
Prostatic Neoplasms: PA, pathology
Raloxifene
Stanolone: PD, pharmacology
Tamoxifen: AA, analogs & derivatives
Testosterone: ME, metabolism
Time Factors
Tumor Cells, Cultured

RN 10540-29-1 (Tamoxifen); 131811-54-6 (EM 139); 13311-84-7 (Flutamide); 25126-76-5 (Androstane-3,17-diol); 50-28-2 (Estradiol); 521-18-6 (Stanolone); 52806-53-8 (hydroxyflutamide); 53-16-7 (Estrone); 57-85-2 (Testosterone); **84449-90-1 (Raloxifene)**; 965-93-5 (Metribolone)
CN 0 (Androgens); 0 (Estrogen Antagonists); 0 (Piperidines)

L44 ANSWER 12 OF 12 CANCERLIT on STN
AN 88296324 CANCERLIT
DN 88296324 PubMed ID: 3402389
TI Mediation by the androgen receptor of the stimulatory and antiandrogenic actions of 17 beta-estradiol on the growth of androgen-sensitive Shionogi mammary carcinoma cells in culture.
AU Luthy I A; Begin D; Labrie F
CS Medical Research Council Group in Molecular Endocrinology, Laval University Medical Center, Quebec, Canada.
SO ENDOCRINOLOGY, (1988 Sep) 123 (3) 1418-24.
Journal code: 0375040. ISSN: 0013-7227.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Abridged Index Medicus Journals; Priority Journals
OS MEDLINE 88296324
EM 198809
ED Entered STN: 19941107
Last Updated on STN: 19970509
AB Increasing concentrations of 17 beta-estradiol (E2) led to a maximal 7-fold stimulation of growth of the highly androgen-sensitive clone (SEM-1) of the mammary carcinoma Shionogi cell line. Half-maximal stimulation by the estrogen was observed at 100 nM E2. Diethylstilbestrol (DES), on the other hand, a synthetic estrogen with no affinity for the androgen receptor, had no significant stimulatory effect on cell growth but caused growth inhibition at concentrations above 1 microM. Mediation of the action of E2 by the androgen receptor is indicated by the absence of interference of E2 action by the antiestrogen LY156758 while the antiandrogen hydroxyflutamide (3 microM) caused a 50% inhibition of E2 action. While increasing concentrations of E2 led to a progressive increase in cell growth, a progressive shift in the ED50 value of action of dihydrotestosterone (DHT) was observed at intermediate (10-100 nM) concentrations of E2 while 10 microM E2 completely inhibited DHT action. At those high E2 concentrations, however, E2 itself led to a stimulation of cell growth equivalent to approximately 50% of the maximal value achieved by DHT. E2 competed with the specific uptake of [3H]testosterone in intact cells at an inhibition constant (Ki) value of 15 nM, thus indicating direct interaction of E2 with the androgen receptor. Preincubation with E2 had no influence on the apparent affinity of testosterone for the androgen receptor nor on the number of androgen

binding sites. The present data demonstrate that both the stimulatory and antiandrogenic action of E2 on the growth of the androgen-sensitive mammary carcinoma cell line SEM-1 are mediated through direct interaction of the estrogen with the androgen receptor. Such data may offer an explanation for the subjective improvements reported in **prostate cancer** patients receiving a high dose of E2 when relapsing after castration.

CT Check Tags: Animal; Male; Support, Non-U.S. Gov't
*Androgen Antagonists
Cell Division: DE, drug effects
Cell Line
Diethylstilbestrol: PD, pharmacology
*Estradiol: PD, pharmacology
Estrogen Antagonists: PD, pharmacology
Kinetics
*Mammary Neoplasms, Experimental: PA, pathology
Mice
Piperidines: PD, pharmacology
Raloxifene
Receptors, Androgen: DE, drug effects
*Receptors, Androgen: PH, physiology
Stanolone: PD, pharmacology
Testosterone: ME, metabolism

RN 50-28-2 (Estradiol); 521-18-6 (Stanolone); 56-53-1 (Diethylstilbestrol); 57-85-2 (Testosterone); **84449-90-1 (Raloxifene)**

CN 0 (Androgen Antagonists); 0 (Estrogen Antagonists); 0 (Piperidines); 0 (Receptors, Androgen)

(2+3) Text


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=> d que l51
L46        45157 SEA FILE=MEDLINE ABB=ON  PLU=ON  PROSTATIC NEOPLASMS+PFT/CT
L49           46 SEA ARZOXIFENE/CN
L50         1441 SEA RALOXIFENE/CN
L51           19 SEA L46 AND (L49 OR L50 OR ARZOXIFENE? OR RALOXIFENE?)


=> d l51 bib ab hitind 1-19

L51  ANSWER 1 OF 19  CANCERLIT on STN
AN   2002190615     CANCERLIT
DN   22219976   PubMed ID: 12235008
TI   Raloxifene, a mixed estrogen agonist/antagonist, induces
     apoptosis in androgen-independent human prostate cancer cell lines.
AU   Kim Isaac Yi; Kim Byung-Chul; Seong Do Hwan; Lee Dug Keun; Seo Jeong-Meen;
     Hong Young Jin; Kim Heung-Tae; Morton Ronald A; Kim Seong-Jin
CS   Laboratory of Cell Regulation and Carcinogenesis, National Cancer
     Institute/NIH, Building 41, Room C629, 9000 Rockville Pike, Bethesda, MD
     20892, USA.
SO   CANCER RESEARCH, (2002 Sep 15) 62 (18) 5365-9.
     Journal code: 2984705R. ISSN: 0008-5472.
CY   United States
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   MEDLINE; Priority Journals
OS   MEDLINE 2002472917
EM   200210
ED   Entered STN: 20021115
     Last Updated on STN: 20021115
AB   Raloxifene, a selective estrogen receptor (ER) modulator, is a
     mixed estrogen agonist/antagonist that has been shown to prevent
     osteoporosis and breast cancer in women. Because the prostate contains
     high levels of ER-beta, the present study investigated the effect of
     raloxifene in three well-characterized, androgen-independent human
     prostate cancer cell lines: (a) PC3; (b) PC3M; and (c) DU145. Reverse
     transcriptase-PCR and Western blot analysis for ER-alpha and ER-beta
     demonstrated that all three cell lines express ER-beta, whereas only PC3
     and PC3M cells were positive for ER-alpha. After the treatment with
     raloxifene, a dramatic increase in cell death was observed in a
     dose-dependent manner in the three prostate cancer cell lines (10(-9) to
     10(-6) M range). Because the three prostate cancer cell lines demonstrated
     similar morphological changes after the raloxifene treatment,
     PC3 (ER-alpha/ER-beta+) and DU145 (ER-beta+ only) cells were selected to
     further characterize the raloxifene-induced cell death. Using
     the nucleus-specific stain 4',6-diamidino-2-phenylindole, nuclear
     fragmentation was observed in a time-dependent manner in both cell lines
     after exposure to 10(-6) M raloxifene. Using the terminal
     deoxynucleotidyl transferase-mediated nick end labeling apoptotic assay,
     it was demonstrated that the nuclear fragmentation was caused by
     apoptosis. To investigate the possibility that caspase activation is
     involved in raloxifene-induced apoptosis, cells were treated
     with the pan-caspase inhibitor ZVAD. The results demonstrated that the
     dramatic change in cellular morphology after treatment with
     raloxifene was no longer observed when cells were pretreated with
     ZVAD. Immunoblot demonstrated activation of caspases 8 and 9 in PC3 and
     DU145 cells, respectively. Taken together, these results demonstrate that
     the mixed estrogen agonist/antagonist, raloxifene, induces
     apoptosis in androgen-independent human prostate cancer cell lines.
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CT Check Tags: Human; Male; Support, U.S. Gov't, P.H.S.
*Apoptosis: DE, drug effects
Neoplasms, Hormone-Dependent: DT, drug therapy
Neoplasms, Hormone-Dependent: PA, pathology
***Prostatic Neoplasms: DT, drug therapy**
Prostatic Neoplasms: PA, pathology
***Raloxifene: PD, pharmacology**
*Selective Estrogen Receptor Modulators: PD, pharmacology
Tumor Cells, Cultured
RN **84449-90-1 (Raloxifene)**
CN 0 (Selective Estrogen Receptor Modulators)

L51 ANSWER 2 OF 19 CANCERLIT on STN
AN 2002169483 CANCERLIT
DN 22091919 PubMed ID: 12097269
TI **Raloxifene**, a selective estrogen receptor modulator, induces apoptosis in androgen-responsive human prostate cancer cell line LNCaP through an androgen-independent pathway.
AU Kim Isaac Yi; Seong Do Hwan; Kim Byung-Chul; Lee Dug Keun; Remaley Alan T; Leach Fredrick; Morton Ronald A; Kim Seong-Jin
CS Laboratory of Cell Regulation and Carcinogenesis, National Cancer Institute, Bethesda, Maryland 20892, USA.
SO CANCER RESEARCH, (2002 Jul 1) 62 (13) 3649-53.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2002353962
EM 200208
ED Entered STN: 20021018
Last Updated on STN: 20021018
AB **Raloxifene**, a selective estrogen receptor (ER) modulator, is a mixed estrogen agonist/antagonist that has been shown to prevent osteoporosis and breast cancer in women. Because the prostate contains a high level of ER-beta, the present study investigated the effect of **raloxifene** in the androgen-sensitive human prostate cancer cell line LNCaP. Previously, it has been demonstrated that LNCaP cells express ER-beta but not ER-alpha and that tamoxifene induces apoptosis in these cells. After treatment with **raloxifene**, a dramatic increase in cell death occurred in a dose-dependent manner (10(-9) to 10(-6) M range). Using the terminal deoxynucleotidyl transferase-mediated nick end labeling apoptotic assay, we demonstrated that the nuclear fragmentation was due to apoptosis. The dramatic change in cellular morphology after treatment with **raloxifene** was no longer observed when cells were pretreated with a pan-caspase inhibitor, Z-VAD-FMK, and a specific caspase-9 inhibitor, Z-LEHD-FMK. Furthermore, immunoblot demonstrated an activation of caspase-9 in LNCaP cells. Because LNCaP cells contain a mutated androgen receptor that allows cellular proliferation in the presence of antiandrogens, prostate-specific antigen assay and transfection with a reporter construct containing luciferase gene under the control of androgen response element (pARE) were carried out. The results demonstrated that **raloxifene** does not significantly alter androgen receptor activity in LNCaP cells. Taken together, these results demonstrate that **raloxifene**, a selective ER modulator, induces apoptosis in the androgen-sensitive human prostate cancer cell line LNCaP through an androgen-independent pathway.
CT Check Tags: Human; Male
*Androgens: PH, physiology

*Apoptosis: DE, drug effects
Apoptosis: PH, physiology
Dose-Response Relationship, Drug
Neoplasms, Hormone-Dependent: DT, drug therapy
*Neoplasms, Hormone-Dependent: PA, pathology
Prostatic Neoplasms: DT, drug therapy
***Prostatic Neoplasms: PA, pathology**
***Raloxifene: PD, pharmacology**
Receptors, Androgen: PH, physiology
*Selective Estrogen Receptor Modulators: PD, pharmacology
Tumor Cells, Cultured
RN **84449-90-1 (Raloxifene)**
CN 0 (Androgens); 0 (Receptors, Androgen); 0 (Selective Estrogen Receptor Modulators)

L51 ANSWER 3 OF 19 CANCERLIT on STN
AN 2002133265 CANCERLIT
DN 21936219 PubMed ID: 11937434
TI Complementary therapies for reducing the risk of osteoporosis in patients receiving luteinizing hormone-releasing hormone treatment/orchiectomy for prostate cancer: a review and assessment of the need for more research.
AU Moyad Mark A
CS Department of Urology, University of Michigan Medical Center, Ann Arbor, Michigan, USA.
SO UROLOGY, (2002 Apr) 59 (4 Suppl 1) 34-40. Ref: 58
Journal code: 0366151. ISSN: 1527-9995.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2002205259
EM 200204
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB Osteoporosis in women has received a substantial amount of attention, but its impact in men is also significant and noteworthy. Those men who benefit from treatment for prostate cancer with androgen deprivation therapy (ADT) may also be at a higher risk for osteoporosis. Pharmacologic approaches to reduce this risk have received some attention. For example, agents such as bisphosphonates, estrogen receptor-binding drugs (diethylstilbestrol, tamoxifen, and **raloxifene**), calcitonin, and fluoride are some of the more promising interventions that have been previously outlined. In addition, statin drugs, or hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, have recently been hypothesized to lower osteoporosis risk. However, complementary therapies, which may also have an impact on reducing osteoporosis risk, have not received attention. Dietary and supplemental calcium and vitamin D have been shown, in some preliminary investigations, to maintain bone density in women and men. Numerous healthy and affordable dietary sources of this mineral and vitamin exist, and large intakes can be realistically achieved through proper education. Similarly, the supplemental dosages required to impact risk have been moderate, appear to be safe, are of low cost, and thus may provide an additional route for reducing risk, especially if these interventions are initiated at the start of medical treatment. More studies in men receiving ADT are needed because the existing work has mostly focused on men without castrate levels of male hormone. Additionally, many studies with conventional and nonconventional

agents have only focused on individuals with baseline osteoporosis, rather than normal bone mineral densities or osteopenia. Other promising complementary therapies, such as weight-bearing exercise and abstaining from smoking, may also be of benefit. Newer estrogenic-type supplements (eg, ipriflavone) appear interesting and have some preliminary data, but more research is desperately required to determine their actual impact and potential for adverse effects (such as lymphocytopenia from a recent trial). Simple, inexpensive, and potentially effective dietary and supplemental approaches to reduce the risk of osteoporosis in men exist, and they should be discussed with patients. Whether these approaches effectively reduce the risk of osteoporosis in men receiving androgen ablation remains to be determined. The possibility is intriguing, and future research is needed. In the meantime, it is important to keep in mind that these complementary approaches are, at the very least, an integral part of the conventional options used today to the reduce the risk of osteoporosis in men and women.

CT Check Tags: Female; Human; Male
Aged
Aged, 80 and over
*Calcium: AD, administration & dosage
Complementary Therapies
*Dietary Supplements
Gonadorelin: AE, adverse effects
Gonadorelin: TU, therapeutic use
Isoflavones: AD, administration & dosage
Life Style
Middle Age
Orchiectomy: AE, adverse effects
Osteoporosis: ET, etiology
*Osteoporosis: PC, prevention & control
***Prostatic Neoplasms: CO, complications**
Prostatic Neoplasms: DT, drug therapy
Risk
*Vitamin D: AD, administration & dosage

RN 1406-16-2 (Vitamin D); 33515-09-2 (Gonadorelin); 35212-22-7 (ipriflavone); 7440-70-2 (Calcium)

CN 0 (Isoflavones)

L51 ANSWER 4 OF 19 CANCERLIT on STN
AN 2002046567 CANCERLIT
DN 21193270 PubMed ID: 11295598
TI Selective estrogen receptor modulators for the chemoprevention of prostate cancer.
AU Steiner M S; Raghow S; Neubauer B L
CS Department of Urology, University of Tennessee, Memphis, Tennessee 38104, USA.. MSteiner@utmem.edu
SO UROLOGY, (2001 Apr) 57 (4 Suppl 1) 68-72.
Journal code: 0366151. ISSN: 1527-9995.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2001265933
EM 200106
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB The ability to interfere with prostate carcinogenesis, and as a consequence, prevent prostate cancer with drugs is the basis for chemoprevention. The prostate contains estrogen receptors in both the

stroma and epithelium. Both animal models and human epidemiologic studies have implicated estrogens as an initiator of prostate cancer. In the aging male, prostate cancer occurs in an environment of rising estrogen and decreasing androgen levels. Selective estrogen receptor modulators (SERMs) have shown the ability to prevent (GTx-006 [acapodene]) and treat (GTx-006 and **arzoxifene**) prostate cancer, suggesting that they may be used in prostate cancer chemoprevention. A phase 2 clinical trial using GTx-006 for prostate cancer chemoprevention is currently being conducted.

CT Check Tags: Human; Male
Age Factors
Androgens: BL, blood
*Anticarcinogenic Agents: TU, therapeutic use
Estrogen Antagonists: PD, pharmacology
Estrogen Receptor Modulators: TU, therapeutic use
Estrogens: BL, blood
Estrogens, Non-Steroidal: PD, pharmacology
Piperidines: PD, pharmacology
Prostate: GD, growth & development
Prostatic Neoplasms: ET, etiology
***Prostatic Neoplasms: PC, prevention & control**
Receptors, Estrogen: PH, physiology
*Selective Estrogen Receptor Modulators: TU, therapeutic use
Tamoxifen: PD, pharmacology
Thiophenes: PD, pharmacology

RN 10540-29-1 (Tamoxifen)

CN 0 (Androgens); 0 (Anticarcinogenic Agents); 0 (Estrogen Antagonists); 0 (Estrogen Receptor Modulators); 0 (Estrogens); 0 (Estrogens, Non-Steroidal); **0 (LY 353381)**; 0 (Piperidines); 0 (Receptors, Estrogen); 0 (Selective Estrogen Receptor Modulators); 0 (Thiophenes); 0 (phytoestrogens)

L51 ANSWER 5 OF 19 CANCERLIT on STN

AN 96347982 CANCERLIT

DN 96347982 PubMed ID: 8757185

TI **Raloxifene**, retinoids, and lavender: "me too" tamoxifen alternatives under study.

AU Ziegler J

SO JOURNAL OF THE NATIONAL CANCER INSTITUTE, (1996 Aug 21) 88 (16) 1100-2. Journal code: 7503089. ISSN: 0027-8874.

CY United States

DT News Announcement

LA English

FS MEDLINE; Priority Journals

OS MEDLINE 96347982

EM 199609

ED Entered STN: 19961008
Last Updated on STN: 19961008

CT Check Tags: Female; Human; Male
Antineoplastic Agents, Hormonal: AE, adverse effects
*Antineoplastic Agents, Hormonal: TU, therapeutic use
Breast Neoplasms: DT, drug therapy
Clinical Trials
Drugs, Investigational: TU, therapeutic use
Estrogen Antagonists: AE, adverse effects
*Estrogen Antagonists: TU, therapeutic use
*Neoplasms: DT, drug therapy
Oils, Volatile: AE, adverse effects
*Oils, Volatile: TU, therapeutic use
Ovarian Neoplasms: DT, drug therapy

Piperidines: AE, adverse effects
*Piperidines: TU, therapeutic use
*Plants, Medicinal
Prostatic Neoplasms: DT, drug therapy
Raloxifene
Retinoids: AE, adverse effects
*Retinoids: TU, therapeutic use
Tamoxifen: AA, analogs & derivatives
Tamoxifen: TU, therapeutic use
Toremifene: TU, therapeutic use
RN 10540-29-1 (Tamoxifen); 116057-75-1 (pyrrolidino-4-iodotamoxifen); 8000-28-0 (lavender oil); 82413-20-5 (3-hydroxytamoxifen); **84449-90-1 (Raloxifene)**; 89778-26-7 (Toremifene)
CN 0 (Antineoplastic Agents, Hormonal); 0 (Drugs, Investigational); 0 (Estrogen Antagonists); 0 (Oils, Volatile); 0 (Piperidines); 0 (Retinoids)

L51 ANSWER 6 OF 19 CANCERLIT on STN
AN 96043753 CANCERLIT
DN 96043753 PubMed ID: 7479389
TI **Raloxifene** (LY156758) produces antimetastatic responses and extends survival in the PAIII rat prostatic adenocarcinoma model.
AU Neubauer B L; Best K L; Counts D F; Goode R L; Hoover D M; Jones C D; Sarosdy M F; Shaar C J; Tanzer L R; Merriman R L
CS Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis 46285, USA.
SO PROSTATE, (1995 Oct) 27 (4) 220-9.
Journal code: 8101368. ISSN: 0270-4137.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 96043753
EM 199512
ED Entered STN: 19960126
Last Updated on STN: 19960126
AB The benzothiophene antiestrogen, **raloxifene** (LY156758), has selective estrogen pharmacological antagonist activity in rats. The PAIII rat prostatic adenocarcinoma model was used to evaluate the effects of this agent on the lymphatic and pulmonary metastasis and survival in tumor-bearing male Lobund-Wistar (LW) rats. **Raloxifene** was inactive against colony formation of PAIII cells in vitro. Similarly, following subcutaneous (s.c.) implantation of 10(6) PAIII cells in the tail, s.c. administration of **raloxifene** (2.0, 10.0, or 20.0 mg/kg/day) for 30 days failed to demonstrate cytoreductive activity against primary tumor growth in the tail. However, in these same animals, **raloxifene** administration produced significant ($P < 0.05$) inhibition of PAIII metastasis from the primary tumor in the tail to the gluteal and iliac lymph nodes (maximal responses = 89% and 81% from control values, respectively). PAIII metastasis to the lungs was significantly inhibited by **raloxifene** treatment. Numbers of pulmonary foci in PAIII-bearing rats were significantly ($P < 0.05$) reduced by **raloxifene** administration in a dose-related manner (maximal reduction = 97% from control values). In these animals, maximal regression of 20% for ventral prostate and 21% for seminal vesicle were also seen after **raloxifene** administration ($P < 0.05$ for both). Coadministration of E2B and **raloxifene** had no consistent antagonistic effect upon the antitumor responses produced by **raloxifene**. **Raloxifene** (40.0 mg/kg/day for 28 days) produced marked decreases in PAIII metastasis in the lymphatic and

pulmonary components. Continued administration of the compound produced significant (P < 0.05) extension of survival of PAIII-bearing rats. Further studies are needed to define the maximal antitumor efficacy and the mechanism of action of **raloxifene** in urogenital solid tumor animal models. These data support the contention that **raloxifene** represents a class of active antimetastatic agents with potential efficacy in the treatment of hormone-insensitive human prostatic cancer.

CT Check Tags: Animal; Male
Adenocarcinoma: DT, drug therapy
Adenocarcinoma: MO, mortality
*Adenocarcinoma: PA, pathology
Adrenal Glands: DE, drug effects
Adrenal Glands: PA, pathology
Antimetabolites, Antineoplastic: PD, pharmacology
Antimetabolites, Antineoplastic: TU, therapeutic use
*Antineoplastic Agents: PD, pharmacology
Antineoplastic Agents: TU, therapeutic use
Disease Models, Animal
Dose-Response Relationship, Drug
Estradiol: PD, pharmacology
Estradiol: TU, therapeutic use
*Estrogen Antagonists: PD, pharmacology
Estrogen Antagonists: TU, therapeutic use
Fluorouracil: PD, pharmacology
Fluorouracil: TU, therapeutic use
Incidence
Lung Neoplasms: EP, epidemiology
Lung Neoplasms: PC, prevention & control
Lung Neoplasms: SC, secondary
Lymphatic Metastasis
Organ Weight: DE, drug effects
*Piperidines: PD, pharmacology
Piperidines: TU, therapeutic use
Prostate: DE, drug effects
Prostate: PA, pathology
Prostatic Neoplasms: DT, drug therapy
Prostatic Neoplasms: MO, mortality
***Prostatic Neoplasms: PA, pathology**
Raloxifene
Random Allocation
Rats
Rats, Wistar
Survival Rate
Testis: DE, drug effects
Testis: PA, pathology
Weight Gain: DE, drug effects

RN 50-28-2 (Estradiol); 51-21-8 (Fluorouracil); **84449-90-1 (Raloxifene)**

CN 0 (Antimetabolites, Antineoplastic); 0 (Antineoplastic Agents); 0 (Estrogen Antagonists); 0 (Piperidines)

L51 ANSWER 7 OF 19 CANCERLIT on STN
AN 92005429 CANCERLIT
DN 92005429 PubMed ID: 1913642
TI Characteristics of the biphasic action of androgens and of the potent antiproliferative effects of the new pure antiestrogen EM-139 on cell cycle kinetic parameters in LNCaP human prostatic cancer cells.
AU de Launoit Y; Veilleux R; Dufour M; Simard J; Labrie F
CS Medical Research Council of Canada Group in Molecular Endocrinology, CHUL

Research Center, Quebec.
SO CANCER RESEARCH, (1991 Oct 1) 51 (19) 5165-70.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 92005429
EM 199110
ED Entered STN: 19941107
Last Updated on STN: 19970509
AB The most potent steroid in human prostatic carcinoma LNCaP cells, i.e., dihydrotestosterone (DHT), has a biphasic stimulatory effect on cell proliferation. At the maximal stimulatory concentration of 0.1 nM DHT, analysis of cell kinetic parameters shows a decrease of the G0-G1 fraction with a corresponding increase of the S and G2 + M fractions. In contrast, concentrations of 1 nM DHT or higher induce a return of cell proliferation to control levels, reflected by an increase in the G0-G1 fraction at the expense of the S and especially the G2 + M fractions. Continuous labeling for 144 h with the nucleotide analogue 5'-bromodeoxyuridine shows that the percentage of cycling LNCaP cells rises more than 90% after treatment with stimulatory concentrations of DHT, whereas in control cells as well as in cells treated with high concentrations of the androgen, this value remains below 50%. Although LNCaP cells do not contain detectable estrogen receptors, the new pure steroidal antiestrogen EM-139 not only reversed the stimulation of cell proliferation and cell kinetics induced by stimulatory doses of DHT but also inhibited basal cell proliferation.
CT Check Tags: Human; In Vitro; Male; Support, Non-U.S. Gov't
*Androgens: PD, pharmacology
Androstane-3,17-diol: PD, pharmacology
Binding, Competitive
*Cell Cycle: DE, drug effects
Dose-Response Relationship, Drug
Drug Antagonism
*Estradiol: AA, analogs & derivatives
Estradiol: PD, pharmacology
*Estrogen Antagonists: PD, pharmacology
Estrone: PD, pharmacology
Flow Cytometry
Flutamide: AA, analogs & derivatives
Flutamide: PD, pharmacology
Metribolone: ME, metabolism
Piperidines: PD, pharmacology
***Prostatic Neoplasms: DT, drug therapy**
Prostatic Neoplasms: PA, pathology
Raloxifene
Stanolone: PD, pharmacology
Tamoxifen: AA, analogs & derivatives
Testosterone: ME, metabolism
Time Factors
Tumor Cells, Cultured
RN 10540-29-1 (Tamoxifen); 131811-54-6 (EM 139); 13311-84-7 (Flutamide); 25126-76-5 (Androstane-3,17-diol); 50-28-2 (Estradiol); 521-18-6 (Stanolone); 52806-53-8 (hydroxyflutamide); 53-16-7 (Estrone); 57-85-2 (Testosterone); **84449-90-1 (Raloxifene)**; 965-93-5 (Metribolone)
CN 0 (Androgens); 0 (Estrogen Antagonists); 0 (Piperidines)

L51 ANSWER 8 OF 19 MEDLINE on STN
AN 2004596348 MEDLINE

DN PubMed ID: 15570061
TI Clinical trials in cancer prevention: current results and perspectives for the future.
AU Greenwald Peter
CS Division of Cancer Prevention, National Cancer Institute, National Institutes of Health, Bethesda, MD 20892, USA.. pg37g@nih.gov
SO Journal of nutrition, (2004 Dec) 134 (12 Suppl) 3507S-3512S. Ref: 46
Journal code: 0404243. ISSN: 0022-3166.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200501
ED Entered STN: 20041201
Last Updated on STN: 20050114
Entered Medline: 20050113
AB Cancer prevention remains the ideal strategy for reducing the burden of cancer on society. Progress in cancer prevention has been accelerated as prevention clinical trials are completed and reported. A promising strategy is the identification of cancer risk factors through epidemiologic and experimental research with lifestyle and medical approaches that allow translation of clinical trial results to clinical practice. A major focus of cancer prevention clinical trials has been on modulation of hormones and nutritional modifications using natural or synthetic bioactive food components for breast and prostate cancer. Breast cancer prevention clinical trials have investigated the role of estrogen antagonists with agents such as tamoxifen, **raloxifene**, and newer agents such as aromatase inhibitors and bioactive food components. Among the promising bioactive food components being investigated at the National Cancer Institute in prevention clinical trials to reduce breast cancer risk are indole-3-carbinol, sulforaphanes, phytoestrogen isoflavones, perillyl alcohol, and green tea polyphenols. Prostate cancer prevention trials have focused on hormone modulation with the 5-alpha-reductase inhibitor finasteride and bioactive food components such as selenium and vitamin E. Soy isoflavones, green tea polyphenols, and doxercalciferol also are being investigated for prostate cancer prevention. Future prevention clinical trials will rely on multidisciplinary medical approaches that bring together expertise in many fields to address disease across the cancer spectrum. Nutritional science can play an important role in this effort through the use of new and emerging technologies to better understand the influence of bioactive food components on the genes, proteins, and cellular processes that are associated with cancer risk.
CT Check Tags: Female; Male
Breast Neoplasms: EP, epidemiology
Breast Neoplasms: PC, prevention & control
*Clinical Trials
Clinical Trials: TD, trends
Diet
Humans
Life Style
Neoplasms: EP, epidemiology
*Neoplasms: PC, prevention & control
Nutrition
Plants, Edible
Prostatic Neoplasms: PC, prevention & control

L51 ANSWER 9 OF 19 MEDLINE on STN
AN 2004388575 MEDLINE
DN PubMed ID: 15292315
TI **Raloxifene** to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer: a randomized controlled trial.
AU Smith Matthew R; Fallon Mary Anne; Lee Hang; Finkelstein Joel S
CS Division of Hematology and Oncology, Massachusetts General Hospital, Boston, Massachusetts 02114, USA.. smith.matthew@mgh.harvard.edu
NC K24 DK02759 (NIDDK)
M01-RR-01066 (NCRR)
SO Journal of clinical endocrinology and metabolism, (2004 Aug) 89 (8) 3841-6.
Journal code: 0375362. ISSN: 0021-972X.
CY United States
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200409
ED Entered STN: 20040805
Last Updated on STN: 20040904
Entered Medline: 20040903
AB GnRH agonists decrease bone mineral density and increase fracture risk in men with prostate cancer. **Raloxifene** increases bone mineral density in postmenopausal women, but its efficacy in hypogonadal men is not known. In a 12-month open-label study, men with nonmetastatic prostate cancer (n = 48) who were receiving a GnRH agonist were assigned randomly to **raloxifene** (60 mg/d) or no **raloxifene**.
Bone mineral densities of the posteroanterior lumbar spine and proximal femur were measured by dual energy x-ray absorptiometry. Mean (+/-se) bone mineral density of the posteroanterior lumbar spine increased by 1.0 +/- 0.9% in men treated with **raloxifene** and decreased by 1.0 +/- 0.6% in men who did not receive **raloxifene** (P = 0.07). Bone mineral density of the total hip increased by 1.1 +/- 0.4% in men treated with **raloxifene** and decreased by 2.6 +/- 0.7% in men who did not receive **raloxifene** (P < 0.001). Similar between-group differences were observed in the femoral neck (P = 0.06) and trochanter (P < 0.001). In men receiving a GnRH agonist, **raloxifene** significantly increases bone mineral density of the hip and tends to increase bone mineral density of the spine.
CT Check Tags: Male
Aged
Biological Markers: BL, blood
Bone Density: DE, drug effects
Bone Remodeling
Double-Blind Method
*Gonadorelin: AG, agonists
Humans
Middle Aged
*Osteoporosis: CI, chemically induced
***Prostatic Neoplasms: DT, drug therapy**
Prostatic Neoplasms: ME, metabolism
Pulmonary Embolism: CI, chemically induced
Raloxifene: AE, adverse effects
***Raloxifene: TU, therapeutic use**
Research Support, Non-U.S. Gov't
Research Support, U.S. Gov't, P.H.S.

*Selective Estrogen Receptor Modulators: TU, therapeutic use
Testosterone: BL, blood
RN 33515-09-2 (Gonadorelin); 58-22-0 (Testosterone); **84449-90-1 (Raloxifene)**
CN 0 (Biological Markers); 0 (Selective Estrogen Receptor Modulators)

L51 ANSWER 10 OF 19 MEDLINE on STN
AN 2004053751 MEDLINE
DN PubMed ID: 14755680
TI Estrogens and anti-estrogens: key mediators of prostate carcinogenesis and new therapeutic candidates.
AU Ho Shuk-Mei
CS Department of Surgery, Division of Urology, University of Massachusetts Medical School, Worcester, Massachusetts 01605, USA.. Shuk-mei.Ho@umassmed.edu
SO Journal of cellular biochemistry, (2004 Feb 15) 91 (3) 491-503. Ref: 163
Journal code: 8205768. ISSN: 0730-2312.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS Priority Journals
EM 200405
ED Entered STN: 20040203
Last Updated on STN: 20040512
Entered Medline: 20040511
AB Despite the historical use of estrogens in the treatment of prostate cancer (PCa) little is known about their direct biological effects on the prostate, their role in carcinogenesis, and what mechanisms mediate their therapeutic effects on PCa. It is now known that estrogens alone, or in synergism with an androgen, are potent inducers of aberrant growth and neoplastic transformation in the prostate. The mechanisms of estrogen carcinogenicity could be mediated via induction of unscheduled cell proliferation or through metabolic activation of estrogens to genotoxic metabolites. Age-related changes and race-/ethnic-based differences in circulating or locally formed estrogens may explain differential PCa risk among different populations. Loss of expression of estrogen receptor (ER)-beta expression during prostate carcinogenesis and prevention of estrogen-mediated oxidative damage could be exploited in future PCa prevention strategies. Re-expression of ER-beta in metastatic PCa cells raises the possibility of using ER-beta-specific ligands in triggering cell death in these malignant cells. A variety of new estrogenic/anti-estrogenic/selective estrogen receptor modulator (SERM)-like compounds, including 2-methoxyestradiol, genistein, resveratrol, licochalcone, **Raloxifene**, ICI 182,780, and estramustine are being evaluated for their potential in the next generation of PCa therapies. Increasing numbers of patients self-medicate with herbal formulations such as PC-SPES. Some of these compounds are selective ER-beta ligands, while most of them have minimal interaction with ER-alpha. Although many may inhibit testosterone production by blockade of the hypothalamal-pituitary-testis axis, the most effective agents also exhibit direct cytostatic, cytotoxic, or apoptotic action on PCa cells. Some of them are potent in interfering with tubulin polymerization, blocking angiogenesis and cell motility, suppressing DNA synthesis, and inhibiting specific kinase activities. Further discovery of other compounds with potent apoptotic activities but minimal estrogen action should promote development of a new generation of effective PCa preventive or treatment regimens with few or no side-effects due to

estrogenicity. Further advancement of our knowledge of the role of estrogens in prostate carcinogenesis through metabolic activation of estrogens and/or ER-mediated pathways will certainly result in better preventive or therapeutic modalities for PCa.

CT Check Tags: Male
*Estrogen Receptor Modulators: TU, therapeutic use
Estrogens: ME, metabolism
*Estrogens: TU, therapeutic use
Gene Expression Regulation, Neoplastic
Humans
Isoflavones: TU, therapeutic use
Phytoestrogens
Plant Preparations: TU, therapeutic use
Prostatic Neoplasms: ET, etiology
Prostatic Neoplasms: GE, genetics
Prostatic Neoplasms: ME, metabolism
***Prostatic Neoplasms: TH, therapy**
Receptors, Estrogen: GE, genetics
Receptors, Estrogen: PH, physiology
CN 0 (Estrogen Receptor Modulators); 0 (Estrogens); 0 (Isoflavones); 0 (Phytoestrogens); 0 (Plant Preparations); 0 (Receptors, Estrogen)

L51 ANSWER 11 OF 19 MEDLINE on STN
AN 2003587846 MEDLINE
DN PubMed ID: 14668987
TI [New insights into the role of estogens and their receptors in prostate cancer].
Neue Einblicke in die Rolle der Ostrogene und ihrer Rezeptoren im Prostatakarzinom.
AU Bonkhoff H; Motherby H; Fixemer T
CS Gemeinschaftspraxis fur Pathologie, Frankfurt/M.. PBonkhoff@t-online.de
SO Der Urologe. Ausg. A, (2003 Dec) 42 (12) 1594-601. Ref: 22
Journal code: 1304110. ISSN: 0340-2592.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA German
FS Priority Journals
EM 200404
ED Entered STN: 20031216
Last Updated on STN: 20040429
Entered Medline: 20040428
AB The present review gives a survey on the differential expression of estrogen receptors alpha and beta (ERalpha, ERbeta) and the progesterone receptor (PR) in human prostate tissue and discusses their potential implications for normal and abnormal prostatic growth. The differentiation compartment of the prostatic epithelium (secretory luminal cells) expresses high levels of ERbeta, while the ERalpha is restricted to the proliferation compartment (basal cells). In high-grade prostatic intraepithelial neoplasia (HGPIN), ERalpha gene expression extends to luminal cells and thus may mediate cancerogenic effects of estrogens on the dysplastic epithelium. Conversely, the ERbeta is downregulated in HGPIN indicating that the chemopreventive effects of phytoestrogens mediated by the ERbeta are partially lost. Irrespective of grades and stages, prostate cancer retains high levels of the ERbeta, which is partially lost in androgen-insensitive stages of the disease. In contrast with breast cancer, the presence of the ERalpha and the progesterone

receptor (PR) is a late event in prostate cancer progression. At least 30% of metastatic and androgen-insensitive tumors express high levels of the PR indicating that these tumors harbor a functional ERalpha. The antiestrogen **raloxifene** has growth-inhibitory effects on androgen-insensitive prostate cancer cells in vitro and induces apoptotic cell death in a dose-dependent fashion. These data provide a rationale for clinical trials to study the efficiency of antiestrogens in the medical treatment of advanced prostate cancer.

CT Check Tags: Male
English Abstract
Estrogen Receptor alpha
Estrogen Receptor beta
*Estrogens: ME, metabolism
Humans
***Prostatic Neoplasms: CL, classification**
***Prostatic Neoplasms: ME, metabolism**
*Receptors, Estrogen: ME, metabolism
*Receptors, Progesterone: ME, metabolism
*Tumor Markers, Biological: ME, metabolism

CN 0 (Estrogen Receptor alpha); 0 (Estrogen Receptor beta); 0 (Estrogens); 0 (Receptors, Estrogen); 0 (Receptors, Progesterone); 0 (Tumor Markers, Biological)

L51 ANSWER 12 OF 19 MEDLINE on STN
AN 2003172584 MEDLINE
DN PubMed ID: 12691266
TI Prevention and early detection clinical trials: opportunities for primary care providers and their patients.
CM Comment in: CA Cancer J Clin. 2003 Mar-Apr;53(2):69-72. PubMed ID: 12691264
AU Ford Leslie G; Minasian Lori M; McCaskill-Stevens Worta; Pisano Etta D; Sullivan Dan; Smith Robert A
CS Division of Cancer Prevention, National Cancer Institute, Bethesda, MD, USA.
SO CA: a cancer journal for clinicians, (2003 Mar-Apr) 53 (2) 82-101. Journal code: 0370647. ISSN: 0007-9235.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Abridged Index Medicus Journals; Priority Journals
EM 200304
ED Entered STN: 20030416
Last Updated on STN: 20030425
Entered Medline: 20030424
AB Enrollment into cancer prevention and early detection clinical trials represents a unique challenge compared with a diagnostic or treatment trial because it involves subjects without a diagnosis of cancer. This paper examines some of the barriers to participation in prevention and early detection trials and provides detailed information about two ongoing prevention and two ongoing early detection clinical trials open to enrollment as well as brief summaries of seven additional trials now open to enrollment.
CT Check Tags: Female; Male
Anticarcinogenic Agents: AE, adverse effects
Anticarcinogenic Agents: TU, therapeutic use
Antioxidants: TU, therapeutic use
Breast Neoplasms: DI, diagnosis
Breast Neoplasms: PC, prevention & control
*Clinical Trials

Humans
*Lung Neoplasms: DI, diagnosis
*Neoplasms: DI, diagnosis
*Neoplasms: PC, prevention & control
Patient Selection
*Primary Health Care
Prostatic Neoplasms: PC, prevention & control
Raloxifene: AE, adverse effects
Raloxifene: TU, therapeutic use
Selenium: TU, therapeutic use
Tamoxifen: AE, adverse effects
Tamoxifen: TU, therapeutic use
Vitamin E: TU, therapeutic use
RN 10540-29-1 (Tamoxifen); 1406-18-4 (Vitamin E); 7782-49-2 (Selenium); **84449-90-1 (Raloxifene)**
CN 0 (Anticarcinogenic Agents); 0 (Antioxidants)

L51 ANSWER 13 OF 19 MEDLINE on STN
AN 2002472917 MEDLINE
DN PubMed ID: 12235008
TI **Raloxifene**, a mixed estrogen agonist/antagonist, induces apoptosis in androgen-independent human prostate cancer cell lines.
AU Kim Isaac Yi; Kim Byung-Chul; Seong Do Hwan; Lee Dug Keun; Seo Jeong-Meen; Hong Young Jin; Kim Heung-Tae; Morton Ronald A; Kim Seong-Jin
CS Laboratory of Cell Regulation and Carcinogenesis, National Cancer Institute/NIH, Building 41, Room C629, 9000 Rockville Pike, Bethesda, MD 20892, USA.
SO Cancer research, (2002 Sep 15) 62 (18) 5365-9.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200210
ED Entered STN: 20020918
Last Updated on STN: 20021010
Entered Medline: 20021008
AB **Raloxifene**, a selective estrogen receptor (ER) modulator, is a mixed estrogen agonist/antagonist that has been shown to prevent osteoporosis and breast cancer in women. Because the prostate contains high levels of ER-beta, the present study investigated the effect of **raloxifene** in three well-characterized, androgen-independent human prostate cancer cell lines: (a) PC3; (b) PC3M; and (c) DU145. Reverse transcriptase-PCR and Western blot analysis for ER-alpha and ER-beta demonstrated that all three cell lines express ER-beta, whereas only PC3 and PC3M cells were positive for ER-alpha. After the treatment with **raloxifene**, a dramatic increase in cell death was observed in a dose-dependent manner in the three prostate cancer cell lines (10(-9) to 10(-6) M range). Because the three prostate cancer cell lines demonstrated similar morphological changes after the **raloxifene** treatment, PC3 (ER-alpha/ER-beta+) and DU145 (ER-beta+ only) cells were selected to further characterize the **raloxifene**-induced cell death. Using the nucleus-specific stain 4',6-diamidino-2-phenylindole, nuclear fragmentation was observed in a time-dependent manner in both cell lines after exposure to 10(-6) M **raloxifene**. Using the terminal deoxynucleotidyl transferase-mediated nick end labeling apoptotic assay, it was demonstrated that the nuclear fragmentation was caused by apoptosis. To investigate the possibility that caspase activation is involved in **raloxifene**-induced apoptosis, cells were treated

with the pan-caspase inhibitor ZVAD. The results demonstrated that the dramatic change in cellular morphology after treatment with **raloxifene** was no longer observed when cells were pretreated with ZVAD. Immunoblot demonstrated activation of caspases 8 and 9 in PC3 and DU145 cells, respectively. Taken together, these results demonstrate that the mixed estrogen agonist/antagonist, **raloxifene**, induces apoptosis in androgen-independent human prostate cancer cell lines.

CT Check Tags: Male
*Apoptosis: DE, drug effects
Humans
Neoplasms, Hormone-Dependent: DT, drug therapy
Neoplasms, Hormone-Dependent: PA, pathology
***Prostatic Neoplasms: DT, drug therapy**
Prostatic Neoplasms: PA, pathology
***Raloxifene: PD, pharmacology**
Research Support, U.S. Gov't, P.H.S.
*Selective Estrogen Receptor Modulators: PD, pharmacology
Tumor Cells, Cultured

RN **84449-90-1 (Raloxifene)**
CN 0 (Selective Estrogen Receptor Modulators)

L51 ANSWER 14 OF 19 MEDLINE on STN
AN 2002353962 MEDLINE
DN PubMed ID: 12097269
TI **Raloxifene**, a selective estrogen receptor modulator, induces apoptosis in androgen-responsive human prostate cancer cell line LNCaP through an androgen-independent pathway.
AU Kim Isaac Yi; Seong Do Hwan; Kim Byung-Chul; Lee Dug Keun; Remaley Alan T; Leach Fredrick; Morton Ronald A; Kim Seong-Jin
CS Laboratory of Cell Regulation and Carcinogenesis, National Cancer Institute, Bethesda, Maryland 20892, USA.
SO Cancer research, (2002 Jul 1) 62 (13) 3649-53.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200208
ED Entered STN: 20020707
Last Updated on STN: 20020809
Entered Medline: 20020808
AB **Raloxifene**, a selective estrogen receptor (ER) modulator, is a mixed estrogen agonist/antagonist that has been shown to prevent osteoporosis and breast cancer in women. Because the prostate contains a high level of ER-beta, the present study investigated the effect of **raloxifene** in the androgen-sensitive human prostate cancer cell line LNCaP. Previously, it has been demonstrated that LNCaP cells express ER-beta but not ER-alpha and that tamoxifene induces apoptosis in these cells. After treatment with **raloxifene**, a dramatic increase in cell death occurred in a dose-dependent manner (10(-9) to 10(-6) M range). Using the terminal deoxynucleotidyl transferase-mediated nick end labeling apoptotic assay, we demonstrated that the nuclear fragmentation was due to apoptosis. The dramatic change in cellular morphology after treatment with **raloxifene** was no longer observed when cells were pretreated with a pan-caspase inhibitor, Z-VAD-FMK, and a specific caspase-9 inhibitor, Z-LEHD-FMK. Furthermore, immunoblot demonstrated an activation of caspase-9 in LNCaP cells. Because LNCaP cells contain a mutated androgen receptor that allows cellular proliferation in the presence of antiandrogens, prostate-specific antigen assay and

transfection with a reporter construct containing luciferase gene under the control of androgen response element (pARE) were carried out. The results demonstrated that **raloxifene** does not significantly alter androgen receptor activity in LNCaP cells. Taken together, these results demonstrate that **raloxifene**, a selective ER modulator, induces apoptosis in the androgen-sensitive human prostate cancer cell line LNCaP through an androgen-independent pathway.

CT Check Tags: Male
*Androgens: PH, physiology
*Apoptosis: DE, drug effects
Apoptosis: PH, physiology
Dose-Response Relationship, Drug
Humans
Neoplasms, Hormone-Dependent: DT, drug therapy
*Neoplasms, Hormone-Dependent: PA, pathology
Prostatic Neoplasms: DT, drug therapy
***Prostatic Neoplasms: PA, pathology**
***Raloxifene: PD, pharmacology**
Receptors, Androgen: PH, physiology
*Selective Estrogen Receptor Modulators: PD, pharmacology
Tumor Cells, Cultured

RN **84449-90-1 (Raloxifene)**

CN 0 (Androgens); 0 (Receptors, Androgen); 0 (Selective Estrogen Receptor Modulators)

L51 ANSWER 15 OF 19 MEDLINE on STN

AN 2002205259 MEDLINE

DN PubMed ID: 11937434

TI Complementary therapies for reducing the risk of osteoporosis in patients receiving luteinizing hormone-releasing hormone treatment/orchiectomy for prostate cancer: a review and assessment of the need for more research.

AU Moyad Mark A

CS Department of Urology, University of Michigan Medical Center, Ann Arbor, Michigan, USA.

SO Urology, (2002 Apr) 59 (4 Suppl 1) 34-40. Ref: 58
Journal code: 0366151. ISSN: 1527-9995.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LA English

FS Priority Journals

EM 200204

ED Entered STN: 20020409
Last Updated on STN: 20020412
Entered Medline: 20020410

AB Osteoporosis in women has received a substantial amount of attention, but its impact in men is also significant and noteworthy. Those men who benefit from treatment for prostate cancer with androgen deprivation therapy (ADT) may also be at a higher risk for osteoporosis. Pharmacologic approaches to reduce this risk have received some attention. For example, agents such as bisphosphonates, estrogen receptor-binding drugs (diethylstilbestrol, tamoxifen, and **raloxifene**), calcitonin, and fluoride are some of the more promising interventions that have been previously outlined. In addition, statin drugs, or hepatic 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, have recently been hypothesized to lower osteoporosis risk. However, complementary therapies, which may also have an impact on reducing osteoporosis risk, have not received attention. Dietary and supplemental calcium and vitamin

D have been shown, in some preliminary investigations, to maintain bone density in women and men. Numerous healthy and affordable dietary sources of this mineral and vitamin exist, and large intakes can be realistically achieved through proper education. Similarly, the supplemental dosages required to impact risk have been moderate, appear to be safe, are of low cost, and thus may provide an additional route for reducing risk, especially if these interventions are initiated at the start of medical treatment. More studies in men receiving ADT are needed because the existing work has mostly focused on men without castrate levels of male hormone. Additionally, many studies with conventional and nonconventional agents have only focused on individuals with baseline osteoporosis, rather than normal bone mineral densities or osteopenia. Other promising complementary therapies, such as weight-bearing exercise and abstaining from smoking, may also be of benefit. Newer estrogenic-type supplements (eg, ipriflavone) appear interesting and have some preliminary data, but more research is desperately required to determine their actual impact and potential for adverse effects (such as lymphocytopenia from a recent trial). Simple, inexpensive, and potentially effective dietary and supplemental approaches to reduce the risk of osteoporosis in men exist, and they should be discussed with patients. Whether these approaches effectively reduce the risk of osteoporosis in men receiving androgen ablation remains to be determined. The possibility is intriguing, and future research is needed. In the meantime, it is important to keep in mind that these complementary approaches are, at the very least, an integral part of the conventional options used today to the reduce the risk of osteoporosis in men and women.

CT Check Tags: Female; Male
Aged
Aged, 80 and over
*Calcium: AD, administration & dosage
Complementary Therapies
*Dietary Supplements
Gonadorelin: AE, adverse effects
Gonadorelin: TU, therapeutic use
Humans
Isoflavones: AD, administration & dosage
Life Style
Middle Aged
Orchiectomy: AE, adverse effects
Osteoporosis: ET, etiology
*Osteoporosis: PC, prevention & control
***Prostatic Neoplasms: CO, complications**
Prostatic Neoplasms: DT, drug therapy
Risk
*Vitamin D: AD, administration & dosage

RN 1406-16-2 (Vitamin D); 33515-09-2 (Gonadorelin); 35212-22-7 (ipriflavone); 7440-70-2 (Calcium)

CN 0 (Isoflavones)

L51 ANSWER 16 OF 19 MEDLINE on STN

AN 2001265933 MEDLINE

DN PubMed ID: 11295598

TI Selective estrogen receptor modulators for the chemoprevention of prostate cancer.

AU Steiner M S; Raghow S; Neubauer B L

CS Department of Urology, University of Tennessee, Memphis, Tennessee 38104, USA.. MSteiner@utmem.edu

SO Urology, (2001 Apr) 57 (4 Suppl 1) 68-72.
Journal code: 0366151. ISSN: 1527-9995.

CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 200106
ED Entered STN: 20010611
Last Updated on STN: 20010611
Entered Medline: 20010607
AB The ability to interfere with prostate carcinogenesis, and as a consequence, prevent prostate cancer with drugs is the basis for chemoprevention. The prostate contains estrogen receptors in both the stroma and epithelium. Both animal models and human epidemiologic studies have implicated estrogens as an initiator of prostate cancer. In the aging male, prostate cancer occurs in an environment of rising estrogen and decreasing androgen levels. Selective estrogen receptor modulators (SERMs) have shown the ability to prevent (GTx-006 [acapodene]) and treat (GTx-006 and **arzoxifene**) prostate cancer, suggesting that they may be used in prostate cancer chemoprevention. A phase 2 clinical trial using GTx-006 for prostate cancer chemoprevention is currently being conducted.
CT Check Tags: Male
Age Factors
Androgens: BL, blood
*Anticarcinogenic Agents: TU, therapeutic use
Estrogen Antagonists: PD, pharmacology
Estrogen Receptor Modulators: TU, therapeutic use
Estrogens: BL, blood
Estrogens, Non-Steroidal: PD, pharmacology
Humans
*Isoflavones
Phytoestrogens
Piperidines: PD, pharmacology
Plant Preparations
Prostate: GD, growth & development
Prostatic Neoplasms: ET, etiology
***Prostatic Neoplasms: PC, prevention & control**
Receptors, Estrogen: PH, physiology
*Selective Estrogen Receptor Modulators: TU, therapeutic use
Tamoxifen: PD, pharmacology
Thiophenes: PD, pharmacology
RN 10540-29-1 (Tamoxifen)
CN 0 (Androgens); 0 (Anticarcinogenic Agents); 0 (Estrogen Antagonists); 0 (Estrogen Receptor Modulators); 0 (Estrogens); 0 (Estrogens, Non-Steroidal); 0 (Isoflavones); **0 (LY 353381)**; 0 (Phytoestrogens); 0 (Piperidines); 0 (Plant Preparations); 0 (Receptors, Estrogen); 0 (Selective Estrogen Receptor Modulators); 0 (Thiophenes)

L51 ANSWER 17 OF 19 MEDLINE on STN
AN 96347982 MEDLINE
DN PubMed ID: 8757185
TI **Raloxifene**, retinoids, and lavender: "me too" tamoxifen alternatives under study.
AU Ziegler J
SO Journal of the National Cancer Institute, (1996 Aug 21) 88 (16) 1100-2.
Journal code: 7503089. ISSN: 0027-8874.
CY United States
DT News Announcement
LA English
FS Priority Journals

EM 199609
ED Entered STN: 19960924
Last Updated on STN: 20000303
Entered Medline: 19960916
CT Check Tags: Female; Male
Antineoplastic Agents, Hormonal: AE, adverse effects
*Antineoplastic Agents, Hormonal: TU, therapeutic use
Breast Neoplasms: DT, drug therapy
Clinical Trials
Drugs, Investigational: TU, therapeutic use
Estrogen Antagonists: AE, adverse effects
*Estrogen Antagonists: TU, therapeutic use
Humans
*Neoplasms: DT, drug therapy
Oils, Volatile: AE, adverse effects
*Oils, Volatile: TU, therapeutic use
Ovarian Neoplasms: DT, drug therapy
Piperidines: AE, adverse effects
*Piperidines: TU, therapeutic use
*Plant Oils
*Plants, Medicinal
Prostatic Neoplasms: DT, drug therapy
Raloxifene
Retinoids: AE, adverse effects
*Retinoids: TU, therapeutic use
Tamoxifen: AA, analogs & derivatives
Tamoxifen: TU, therapeutic use
Toremifene: TU, therapeutic use
RN 10540-29-1 (Tamoxifen); 116057-75-1 (pyrrolidino-4-iodotamoxifen); 8000-28-0 (lavender oil); 82413-20-5 (3-hydroxytamoxifen); **84449-90-1 (Raloxifene)**; 89778-26-7 (Toremifene)
CN 0 (Antineoplastic Agents, Hormonal); 0 (Drugs, Investigational); 0 (Estrogen Antagonists); 0 (Oils, Volatile); 0 (Piperidines); 0 (Plant Oils); 0 (Retinoids)

L51 ANSWER 18 OF 19 MEDLINE on STN
AN 96043753 MEDLINE
DN PubMed ID: 7479389
TI **Raloxifene** (LY156758) produces antimetastatic responses and extends survival in the PAIII rat prostatic adenocarcinoma model.
AU Neubauer B L; Best K L; Counts D F; Goode R L; Hoover D M; Jones C D; Sarosdy M F; Shaar C J; Tanzer L R; Merriman R L
CS Lilly Research Laboratories, Eli Lilly and Company, Lilly Corporate Center, Indianapolis 46285, USA.
SO Prostate, (1995 Oct) 27 (4) 220-9.
Journal code: 8101368. ISSN: 0270-4137.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199512
ED Entered STN: 19960124
Last Updated on STN: 20000303
Entered Medline: 19951204
AB The benzothiophene antiestrogen, **raloxifene** (LY156758), has selective estrogen pharmacological antagonist activity in rats. The PAIII rat prostatic adenocarcinoma model was used to evaluate the effects of this agent on the lymphatic and pulmonary metastasis and survival in tumor-bearing male Lobund-Wistar (LW) rats. **Raloxifene** was

inactive against colony formation of PAIII cells in vitro. Similarly, following subcutaneous (s.c.) implantation of 10(6) PAIII cells in the tail, s.c. administration of **raloxifene** (2.0, 10.0, or 20.0 mg/kg/day) for 30 days failed to demonstrate cytoreductive activity against primary tumor growth in the tail. However, in these same animals, **raloxifene** administration produced significant ($P < 0.05$) inhibition of PAIII metastasis from the primary tumor in the tail to the gluteal and iliac lymph nodes (maximal responses = 89% and 81% from control values, respectively). PAIII metastasis to the lungs was significantly inhibited by **raloxifene** treatment. Numbers of pulmonary foci in PAIII-bearing rats were significantly ($P < 0.05$) reduced by **raloxifene** administration in a dose-related manner (maximal reduction = 97% from control values). In these animals, maximal regression of 20% for ventral prostate and 21% for seminal vesicle were also seen after **raloxifene** administration ($P < 0.05$ for both). Coadministration of E2B and **raloxifene** had no consistent antagonistic effect upon the antitumor responses produced by **raloxifene**. **Raloxifene** (40.0 mg/kg/day for 28 days) produced marked decreases in PAIII metastasis in the lymphatic and pulmonary components. Continued administration of the compound produced significant ($P < 0.05$) extension of survival of PAIII-bearing rats. Further studies are needed to define the maximal antitumor efficacy and the mechanism of action of **raloxifene** in urogenital solid tumor animal models. These data support the contention that **raloxifene** represents a class of active antimetastatic agents with potential efficacy in the treatment of hormone-insensitive human prostatic cancer.

CT Check Tags: Male
Adenocarcinoma: DT, drug therapy
Adenocarcinoma: MO, mortality
*Adenocarcinoma: PA, pathology
Adrenal Glands: DE, drug effects
Adrenal Glands: PA, pathology
Animals
Antimetabolites, Antineoplastic: PD, pharmacology
Antimetabolites, Antineoplastic: TU, therapeutic use
*Antineoplastic Agents: PD, pharmacology
Antineoplastic Agents: TU, therapeutic use
Disease Models, Animal
Dose-Response Relationship, Drug
Estradiol: PD, pharmacology
Estradiol: TU, therapeutic use
*Estrogen Antagonists: PD, pharmacology
Estrogen Antagonists: TU, therapeutic use
Fluorouracil: PD, pharmacology
Fluorouracil: TU, therapeutic use
Incidence
Lung Neoplasms: EP, epidemiology
Lung Neoplasms: PC, prevention & control
Lung Neoplasms: SC, secondary
Lymphatic Metastasis
Organ Size: DE, drug effects
*Piperidines: PD, pharmacology
Piperidines: TU, therapeutic use
Prostate: DE, drug effects
Prostate: PA, pathology
Prostatic Neoplasms: DT, drug therapy
Prostatic Neoplasms: MO, mortality
***Prostatic Neoplasms: PA, pathology**
Raloxifene

Random Allocation
Rats
Rats, Wistar
Survival Rate
Testis: DE, drug effects
Testis: PA, pathology
Weight Gain: DE, drug effects

RN 50-28-2 (Estradiol); 51-21-8 (Fluorouracil); **84449-90-1 (Raloxifene)**

CN 0 (Antimetabolites, Antineoplastic); 0 (Antineoplastic Agents); 0 (Estrogen Antagonists); 0 (Piperidines)

L51 ANSWER 19 OF 19 MEDLINE on STN
AN 92005429 MEDLINE
DN PubMed ID: 1913642
TI Characteristics of the biphasic action of androgens and of the potent antiproliferative effects of the new pure antiestrogen EM-139 on cell cycle kinetic parameters in LNCaP human prostatic cancer cells.
AU de Launoit Y; Veilleux R; Dufour M; Simard J; Labrie F
CS Medical Research Council of Canada Group in Molecular Endocrinology, CHUL Research Center, Quebec.
SO Cancer research, (1991 Oct 1) 51 (19) 5165-70.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS Priority Journals
EM 199110
ED Entered STN: 19920124
Last Updated on STN: 20000303
Entered Medline: 19911029
AB The most potent steroid in human prostatic carcinoma LNCaP cells, i.e., dihydrotestosterone (DHT), has a biphasic stimulatory effect on cell proliferation. At the maximal stimulatory concentration of 0.1 nM DHT, analysis of cell kinetic parameters shows a decrease of the G0-G1 fraction with a corresponding increase of the S and G2 + M fractions. In contrast, concentrations of 1 nM DHT or higher induce a return of cell proliferation to control levels, reflected by an increase in the G0-G1 fraction at the expense of the S and especially the G2 + M fractions. Continuous labeling for 144 h with the nucleotide analogue 5'-bromodeoxyuridine shows that the percentage of cycling LNCaP cells rises more than 90% after treatment with stimulatory concentrations of DHT, whereas in control cells as well as in cells treated with high concentrations of the androgen, this value remains below 50%. Although LNCaP cells do not contain detectable estrogen receptors, the new pure steroidal antiestrogen EM-139 not only reversed the stimulation of cell proliferation and cell kinetics induced by stimulatory doses of DHT but also inhibited basal cell proliferation.
CT Check Tags: In Vitro; Male
*Androgens: PD, pharmacology
Androstane-3,17-diol: PD, pharmacology
Binding, Competitive
*Cell Cycle: DE, drug effects
Dihydrotestosterone: PD, pharmacology
Dose-Response Relationship, Drug
Drug Antagonism
*Estradiol: AA, analogs & derivatives
Estradiol: PD, pharmacology
*Estrogen Antagonists: PD, pharmacology
Estrone: PD, pharmacology

Flow Cytometry
Flutamide: AA, analogs & derivatives
Flutamide: PD, pharmacology
Humans
Metribolone: ME, metabolism
Piperidines: PD, pharmacology
***Prostatic Neoplasms: DT, drug therapy**
Prostatic Neoplasms: PA, pathology
Raloxifene
Research Support, Non-U.S. Gov't
Tamoxifen: AA, analogs & derivatives
Testosterone: ME, metabolism
Time Factors
Tumor Cells, Cultured

RN 10540-29-1 (Tamoxifen); 131811-54-6 (EM 139); 13311-84-7 (Flutamide); 25126-76-5 (Androstane-3,17-diol); 50-28-2 (Estradiol); 521-18-6 (Dihydrotestosterone); 52806-53-8 (hydroxyflutamide); 53-16-7 (Estrone); 58-22-0 (Testosterone); **84449-90-1 (Raloxifene)**; 965-93-5 (Metribolone)

CN 0 (Androgens); 0 (Estrogen Antagonists); 0 (Piperidines)

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     (FILE 'HOME' ENTERED AT 08:51:13 ON 02 MAY 2005)

     FILE 'HCAPLUS' ENTERED AT 08:51:19 ON 02 MAY 2005
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               E US2003-625152/APPS
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               SEL RN

     FILE 'REGISTRY' ENTERED AT 08:52:35 ON 02 MAY 2005
L2            16 SEA ABB=ON  PLU=ON  (176672-18-7/BI OR 50-28-2/BI OR 716847-66-
               4/BI OR 716847-67-5/BI OR 716847-68-6/BI OR 716847-69-7/BI OR
               716847-70-0/BI OR 716847-71-1/BI OR 716847-72-2/BI OR 716847-73
               -3/BI OR 716847-74-4/BI OR 716847-75-5/BI OR 716847-76-6/BI OR
               716847-77-7/BI OR 82640-04-8/BI OR 84449-90-1/BI)

     FILE 'HCAPLUS' ENTERED AT 08:52:42 ON 02 MAY 2005
L3             1 SEA ABB=ON  PLU=ON  L1 AND L2
               D IALL HITSTR
               E PROSTATE CANCER/CT
               E E3+ALL
               E E2+ALL
L4          1941 SEA ABB=ON  PLU=ON  "PROSTATE GLAND, NEOPLASM"+PFT,NT/CT(L)ANDR
               OGEN
L5           444 SEA ABB=ON  PLU=ON  "PROSTATE GLAND, NEOPLASM"+PFT,NT/CT(L)INDE
               PENDENT
L6           352 SEA ABB=ON  PLU=ON  "PROSTATE GLAND, NEOPLASM"+PFT,NT/CT(L)DEPE
               NDENT
L7           372 SEA ABB=ON  PLU=ON  L4 AND L5
L8           138 SEA ABB=ON  PLU=ON  L4 AND L6
L9            32 SEA ABB=ON  PLU=ON  L7 AND REVIEW/DT
L10            8 SEA ABB=ON  PLU=ON  L8 AND REVIEW/DT
               D QUE L9
               D L9 IBIB ABS HITIND 1-32
               D QUE L10
               D L10 IBIB ABS HITIND 1-8

     FILE 'CANCERLIT' ENTERED AT 09:10:14 ON 02 MAY 2005
               E ANDROGEN INDEPENDENT/CT
               E PROSTATE CANCER/CT
               E E3+ALL
               E E2+ALL
L11            0 SEA ABB=ON  PLU=ON  PROSTATIC NEOPLASMS+PFT/CT(L)ADROGEN?
L12            0 SEA ABB=ON  PLU=ON  PROSTATIC NEOPLASMS+PFT/CT(L)ANDROGEN?
L13        34951 SEA ABB=ON  PLU=ON  PROSTATIC NEOPLASMS+PFT/CT OR PROSTATE
               CANCER
L14          890 SEA ABB=ON  PLU=ON  L13 AND ANDROGEN INDEPEND?
               D KWIC
L15        31288 SEA ABB=ON  PLU=ON  PROSTATIC NEOPLASMS+PFT/CT
L16          720 SEA ABB=ON  PLU=ON  L15 AND ANDROGEN INDEPENDENT
L17          452 SEA ABB=ON  PLU=ON  L15 AND ANDROGEN DEPENDENT
               D KWIC
L18         3763 SEA ABB=ON  PLU=ON  PROSTATIC NEOPLASMS+PFT/CT(L)TH
               D KWIC
L19           78 SEA ABB=ON  PLU=ON  L18 AND L16
L20           48 SEA ABB=ON  PLU=ON  L18 AND L17
               D QUE L19
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                D L19 BIB ABS HITIND 1-20
                D QUE L19
                D L19 BIB AB HITIND 1-78
                D QUE L20
                D L20 BIB AB HITIND 1-48
L21          17 SEA ABB=ON  PLU=ON  L20 AND REVIEW/DT

     FILE 'REGISTRY' ENTERED AT 09:18:23 ON 02 MAY 2005
L22             STR
L23          16 SEA SSS SAM L22
L24         359 SEA SSS FUL L22

     FILE 'HCAPLUS' ENTERED AT 09:23:40 ON 02 MAY 2005
L25        1408 SEA ABB=ON  PLU=ON  L24
L26        1159 SEA ABB=ON  PLU=ON  L24(L)(BAC OR DMA OR PAC OR PKT OR THU)/RL

L27       19177 SEA ABB=ON  PLU=ON  "PROSTATE GLAND, NEOPLASM"+PFT,NT/CT
L28          80 SEA ABB=ON  PLU=ON  L26 AND L27
L29           2 SEA ABB=ON  PLU=ON  L26 AND L5
L30           5 SEA ABB=ON  PLU=ON  L26 AND L6
L31           7 SEA ABB=ON  PLU=ON  L29 OR L30
                D QUE L31
L32           8 SEA ABB=ON  PLU=ON  L28 AND ANDROGEN(3A)?DEPEND?
L33          11 SEA ABB=ON  PLU=ON  L31 OR L32
                D QUE
                D L33 IBIB ABS HITIND HITSTR 1-11

     FILE 'CANCERLIT' ENTERED AT 09:27:39 ON 02 MAY 2005
L34         320 SEA ABB=ON  PLU=ON  L24
L35           0 SEA ABB=ON  PLU=ON  L24(L)TH
L36           0 SEA ABB=ON  PLU=ON  L34 AND L4
L37           8 SEA ABB=ON  PLU=ON  L34 AND L13
                E ARZOXIFENE/CN
                E E3+ALL
                E E2+ALL
L38          11 SEA ABB=ON  PLU=ON  "LY 353381"+PFT/CN
L39          13 SEA ABB=ON  PLU=ON  L38 OR ARZOXIFENE
                E RALOXIFENE/CN
                E E3+ALL
L40         409 SEA ABB=ON  PLU=ON  RALOXIFENE/CN OR RALOXIFENE?
L41           1 SEA ABB=ON  PLU=ON  L39 AND L13
L42          11 SEA ABB=ON  PLU=ON  L40 AND L13
L43          12 SEA ABB=ON  PLU=ON  L33 OR L41 OR L42
L44          12 SEA ABB=ON  PLU=ON  L37 OR L41 OR L42
                D QUE
                D L44 BIB AB HITIND 1-12

     FILE 'MEDLINE' ENTERED AT 09:34:20 ON 02 MAY 2005
L45        1124 SEA ABB=ON  PLU=ON  L24
                E PROSTATE CANCER/CT
                E E3+ALL
                E E2+ALL
L46       45157 SEA ABB=ON  PLU=ON  PROSTATIC NEOPLASMS+PFT/CT
L47           7 SEA ABB=ON  PLU=ON  L46 AND L45

     FILE 'CANCERLIT, MEDLINE' ENTERED AT 09:35:35 ON 02 MAY 2005
L48          14 DUP REM L44 L47 (5 DUPLICATES REMOVED)
                    ANSWERS '1-12' FROM FILE CANCERLIT
                    ANSWERS '13-14' FROM FILE MEDLINE
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                E ARZOXIFENE/CN
                E E3+ALL
L49           46 SEA ABB=ON  PLU=ON  ARZOXIFENE/CN
                E RALOXIFENE/CN
L50         1441 SEA ABB=ON  PLU=ON  RALOXIFENE/CN
L51           19 SEA ABB=ON  PLU=ON  L46 AND (L49 OR L50 OR ARZOXIFENE? OR
                RALOXIFENE?)
                D QUE L51
                D L51 BIB AB HITIND 1-19
L52            0 SEA ABB=ON  PLU=ON  L47 NOT L51
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FILE HOME

FILE HCAPLUS

FILE COVERS 1907 - 2 May 2005 VOL 142 ISS 19
FILE LAST UPDATED: 1 May 2005 (20050501/ED)

New CAS Information Use Policies, enter HELP USAGETERMS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE REGISTRY
Property values tagged with IC are from the ZIC/VINITI data file provided by InfoChem.

STRUCTURE FILE UPDATES: 1 MAY 2005 HIGHEST RN 849587-91-3
DICTIONARY FILE UPDATES: 1 MAY 2005 HIGHEST RN 849587-91-3

New CAS Information Use Policies, enter HELP USAGETERMS for details.

TSCA INFORMATION NOW CURRENT THROUGH JANUARY 18, 2005

Please note that search-term pricing does apply when conducting SmartSELECT searches.

```
**********************************************************************
*                                                                    *
* The CA roles and document type information have been removed from  *
* the IDE default display format and the ED field has been added,    *
* effective March 20, 2005.  A new display format, IDERL, is now     *
* available and contains the CA role and document type information.  *
*                                                                    *
**********************************************************************
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Crossover limits have been increased. See HELP CROSSOVER for details.

Experimental and calculated property data are now available. For more information enter HELP PROP at an arrow prompt in the file or refer to the file summary sheet on the web at:
http://www.cas.org/ONLINE/DBSS/registryss.html

FILE CANCERLIT
FILE COVERS 1963 TO 15 Nov 2002 (20021115/ED)

On July 28, 2002, CANCERLIT was reloaded. See HELP RLOAD for details.

CANCERLIT thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2002 vocabulary. Enter HELP THESAURUS for details.

This file contains CAS Registry Numbers for easy and accurate substance identification.

FILE MEDLINE
FILE LAST UPDATED: 30 APR 2005 (20050430/UP). FILE COVERS 1950 TO DATE.

On December 19, 2004, the 2005 MeSH terms were loaded.

The MEDLINE reload for 2005 is now available. For details enter HELP RLOAD at an arrow promt (=>). See also:

http://www.nlm.nih.gov/mesh/
http://www.nlm.nih.gov/pubs/techbull/nd04/nd04_mesh.html

OLDMEDLINE now back to 1950.

MEDLINE thesauri in the /CN, /CT, and /MN fields incorporate the MeSH 2005 vocabulary.

This file contains CAS Registry Numbers for easy and accurate substance identification.

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L5          444 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "PROSTATE GLAND, NEOPLASM"+PFT
                ,NT/CT(L)INDEPENDENT
L6          352 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "PROSTATE GLAND, NEOPLASM"+PFT
                ,NT/CT(L)DEPENDENT
L22             STR
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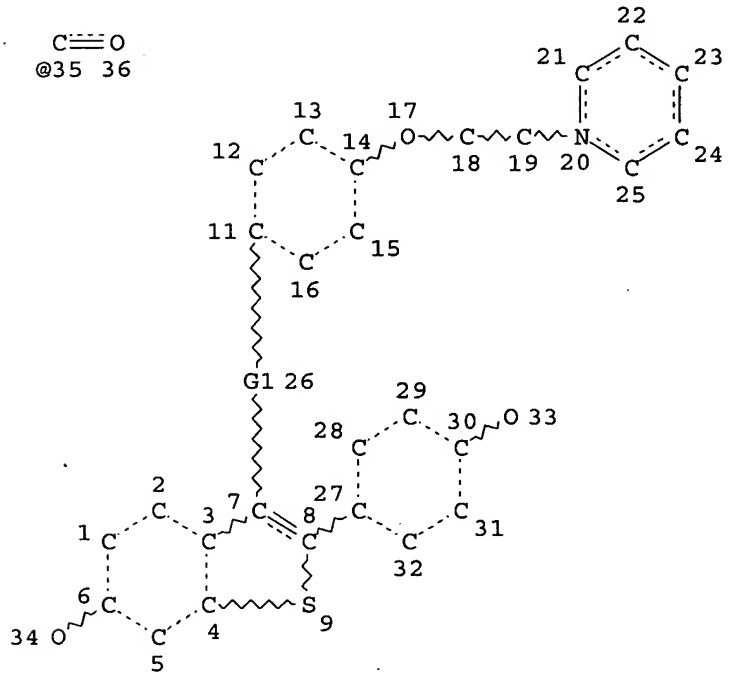


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VAR G1=O/35
NODE ATTRIBUTES:
DEFAULT MLEVEL IS ATOM
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS  35

STEREO ATTRIBUTES: NONE
L24          359 SEA FILE=REGISTRY SSS FUL L22
L26         1159 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L24(L)(BAC OR DMA OR PAC OR
                 PKT OR THU)/RL
L27        19177 SEA FILE=HCAPLUS ABB=ON  PLU=ON  "PROSTATE GLAND, NEOPLASM"+PFT
                 ,NT/CT
L28           80 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L26 AND L27
L29            2 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L26 AND L5
L30            5 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L26 AND L6
L31            7 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L29 OR L30
L32            8 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L28 AND ANDROGEN(3A)?DEPEND?
L33           11 SEA FILE=HCAPLUS ABB=ON  PLU=ON  L31 OR L32

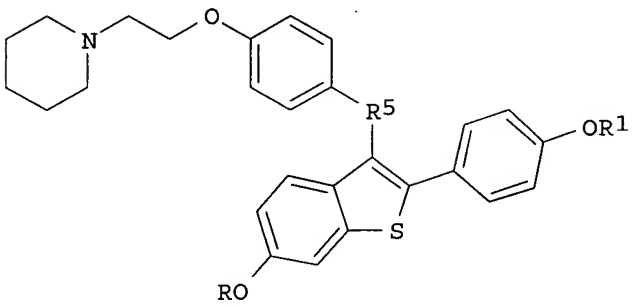

=> d l33 ibib abs hitind hitstr 1-11

L33  ANSWER 1 OF 11  HCAPLUS  COPYRIGHT 2005 ACS on STN
```

ACCESSION NUMBER: 2004:550743 HCAPLUS
DOCUMENT NUMBER: 141:82310
TITLE: Use of benzothiophenes and optional estrogen-lowering agents to treat and prevent prostate cancer
INVENTOR(S): Agus, David B.
PATENT ASSIGNEE(S): Cedars-Sinai Medical Center, USA
SOURCE: U.S. Pat. Appl. Publ., 21 pp., Cont.-in-part of U.S. Pat. Appl. 2002 198,235.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.		DATE
US 2004132776	A1	20040708	US 2003-625152		20030723
US 2002198235	A1	20021226	US 2002-142087		20020509
PRIORITY APPLN. INFO.:			US 2002-142087	A2	20020509
			US 2001-290307P	P	20010510

OTHER SOURCE(S): MARPAT 141:82310
GI



I

AB A method is disclosed for treating and preventing prostate cancer, particularly **androgen-independent** prostate cancer, the method including administering to a mammal a benzothiopene I (R, R1 = H, COR2, COR3, R4; R2 = H, C1-14 alkyl, C1-3 chloroalkyl, C1-3 fluoroalkyl, C5-7 cycloalkyl, C1-4 alkoxy, Ph; R3 = substituted Ph; R4 = C1-4 alkyl, C5-7 cycloalkyl, benzyl; R5 = O, C=O), or pharmaceutically acceptable salts or prodrugs thereof. The method may further include the administration of an estrogen-lowering drug to enhance efficacy of the compound of the invention.

IC ICM A61K031-453
INCL 514320000
CC 1-6 (Pharmacology)
IT **Androgens**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**androgen-independent** prostate cancer; benzothiophenes and optional estrogen-lowering agents for treatment and prevention of prostate cancer)
IT Antitumor agents
Drug toxicity

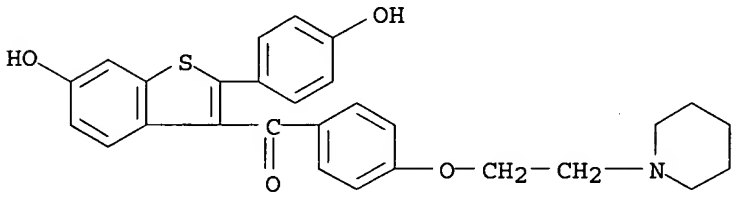
Human
Prostate gland, neoplasm
(benzothiophenes and optional estrogen-lowering agents for treatment and prevention of prostate cancer)

IT **84449-90-1**
RL: ADV (Adverse effect, including toxicity); **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(benzothiophenes and optional estrogen-lowering agents for treatment and prevention of prostate cancer)

IT **82640-04-8**, Raloxifene hydrochloride **176672-18-7**
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(benzothiophenes and optional estrogen-lowering agents for treatment and prevention of prostate cancer)

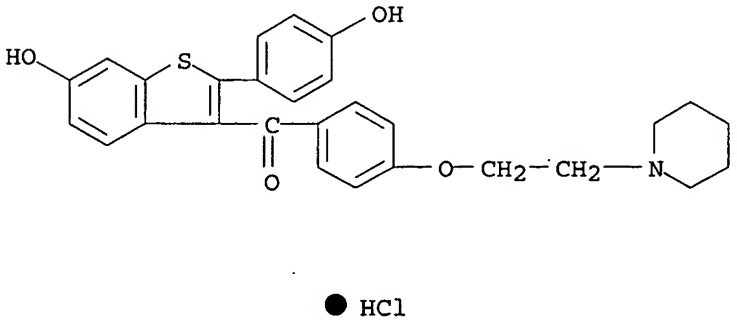
IT **84449-90-1**
RL: ADV (Adverse effect, including toxicity); **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(benzothiophenes and optional estrogen-lowering agents for treatment and prevention of prostate cancer)

RN 84449-90-1 HCAPLUS
CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



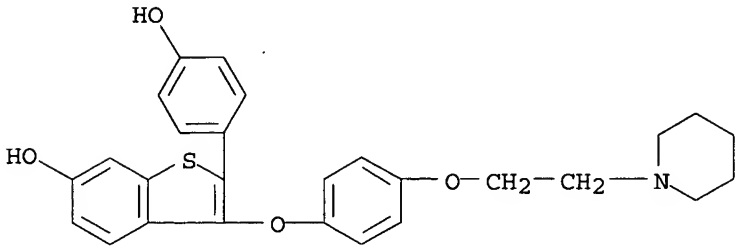
IT **82640-04-8**, Raloxifene hydrochloride **176672-18-7**
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(benzothiophenes and optional estrogen-lowering agents for treatment and prevention of prostate cancer)

RN 82640-04-8 HCAPLUS
CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]-, hydrochloride (9CI) (CA INDEX NAME)



RN 176672-18-7 HCAPLUS

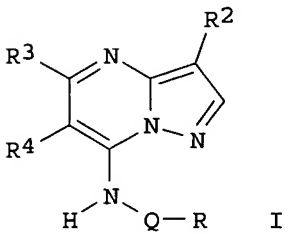
CN Benzo[b]thiophene-6-ol, 2-(4-hydroxyphenyl)-3-[4-[2-(1-piperidinyl)ethoxy]phenoxy]- (9CI) (CA INDEX NAME)



L33 ANSWER 2 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:220335 HCAPLUS
DOCUMENT NUMBER: 140:270872
TITLE: Preparation of pyrazolo[1,5-a]pyrimidines as cyclin dependent kinase inhibitors and anticancer agents
INVENTOR(S): Guzi, Timothy J.; Paruch, Kamil; Dwyer, Michael P.; Doll, Ronald J.; Girijavallabhan, Viyyoor Moopil; Dillard, Lawrence W.; Tran, Vinh D.; He, Zhen Min; James, Ray Anthony; Park, Haengsoon
PATENT ASSIGNEE(S): Schering Corporation, USA; Pharmacopeia, Inc.
SOURCE: PCT Int. Appl., 82 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004022560	A1	20040318	WO 2003-US27502	20030903
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NI, NO, NZ, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004116442	A1	20040617	US 2003-653868	20030903

PRIORITY APPLN. INFO.: US 2002-407999P P 20020904
OTHER SOURCE(S): MARPAT 140:270872
GI



I

AB The title compds. [I; Q = SO2, CO; R = each (un)substituted aryl or heteroaryl; R2 = cyano, NR5R6, CO2R6, CONR5R6, OR6, SR6, SO2R7, SO2NR5R6, -N(R5)SO2R7, N(R5)COR7, N(R5)CONR5R6, alkynyl, heteroaryl, CF3, heterocyclyl, alkynylalkyl, cycloalkyl, (un)substituted alkyl; R3 = H, halogen, NR5R6, CONR5R6, each (un)substituted alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, etc.; R4 = H, halo, alkyl; R5 = H, alkyl; R6 = H, each (un)substituted alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; or R5 and R6 in the moiety -NR5R6, may be joined together to form an (un)substituted cycloalkyl or heterocyclyl] or pharmaceutically acceptable salts or solvates thereof are prepared In its many embodiments, the present invention also provides methods of preparing such compds., pharmaceutical compns. containing one or more such compds. I, methods of preparing pharmaceutical formulations comprising one or more such compds., and methods of treatment, prevention, inhibition, or amelioration of one or more diseases associated with cyclin dependent kinase using such compds. I or pharmaceutical compns. The disease associated with cyclin dependent kinase is selected from the group consisting of; (1) cancer of the bladder, breast, colon, kidney, liver, lung, small cell lung cancer, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; (2) leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkitt's lymphoma; (3) acute and chronic myelogenous leukemia, myelodysplastic syndrome and promyelocytic leukemia; (4) fibrosarcoma and rhabdomyosarcoma; (5) astrocytoma, neuroblastoma, glioma and schwannomas; and (6) melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoacanthoma, thyroid follicular cancer and Kaposi's sarcoma.

IC ICM C07D487-04
ICS A61K031-519; A61P025-00; A61P035-00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 7

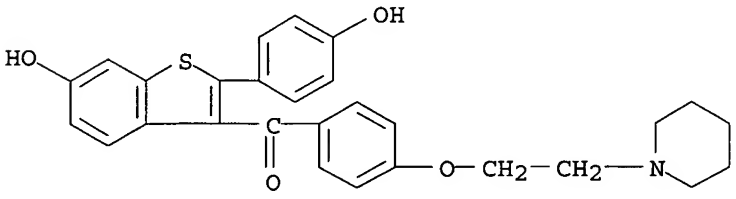
IT Antitumor agents
Bladder, neoplasm
Esophagus, neoplasm
Gallbladder, neoplasm
Hodgkin's disease
Kidney, neoplasm
Leukemia
Liver, neoplasm
Lung, neoplasm
Mammary gland, neoplasm
Melanoma
Myelodysplastic syndromes
Neoplasm
Neuroglia, neoplasm
Ovary, neoplasm
Pancreas, neoplasm
Prostate gland, neoplasm
Skin, neoplasm
Stomach, neoplasm
Thyroid gland, neoplasm
(preparation of pyrazolo[1,5-a]pyrimidines as cyclin **dependent** kinase inhibitors and anticancer agents)

IT 50-07-7, Mitomycin-C 50-18-0, Cyclophosphamide 50-24-8, Prednisolone
50-44-2, 6-Mercaptopurine 50-76-0, Dactinomycin 50-91-9, Floxuridine

51-18-3, Triethylenemelamine 51-21-8, 5-Fluorouracil 51-75-2
52-24-4, Triethylenethiophosphoramide 53-03-2, Prednisone 53-19-0,
Mitotane 54-91-1, Pipobroman 55-98-1, Busulfan 56-53-1,
Diethylstilbestrol 57-22-7, Vincristine 57-63-6, 17α-
Ethynylestradiol 58-05-9, Leucovorin 58-18-4, Methyltestosterone
58-22-0, Testosterone 59-05-2, Methotrexate 66-75-1, Uracil mustard
68-96-2, Hydroxyprogesterone 71-58-9, Medroxyprogesteroneacetate
76-43-7, Fluoxymesterone 83-43-2, Methylprednisolone 124-94-7,
Triamcinolone 125-84-8, Aminoglutethimide 127-07-1, Hydroxyurea
147-94-4, Ara-C 148-82-3, Melphalan 154-42-7, 6-Thioguanine
154-93-8, Carmustine 305-03-3, Chlorambucil 521-12-0, Dromostanolone
propionate 569-57-3, Chlorotrianisene 595-33-5, Megestrolacetate
645-05-6, Hexamethylmelamine 671-16-9, Procarbazine 865-21-4,
Vinblastine 968-93-4, Testolactone 2998-57-4, Estramustine
3778-73-2, Ifosfamide 4342-03-4, Dacarbazine 9015-68-3, L-Asparaginase
10540-29-1, Tamoxifen 11056-06-7, Bleomycin 13010-47-4, Lomustine
13311-84-7, Flutamide 14769-73-4, Levamisole 15663-27-1, Cisplatin
18378-89-7, Mithramycin 18883-66-4, Streptozocin 20830-81-3,
Daunorubicin 23214-92-8, Doxorubicin 25316-40-9, Adriamycin
29767-20-2, Teniposide 33069-62-4, Taxol 33419-42-0, Etoposide
41575-94-4, Carboplatin 51264-14-3, Amsacrine 53643-48-4, Vindesine
53714-56-0, Leuprolide 53910-25-1, Pentostatin 56420-45-2, Epirubicin
58957-92-9, Idarubicin 61825-94-3, Oxaliplatin 65271-80-9,
Mitoxantrone 65807-02-5, Goserelin 75607-67-9, Fludarabine phosphate
82413-20-5, Droloxifene **84449-90-1**, Raloxifene 85622-93-1,
Temozolomide 89778-26-7, Toremifene 95058-81-4, Gemcitabine
97682-44-5, Irinotecan 100286-90-6, CPT-11 114977-28-5, Taxotere
120511-73-1, Anastrozole 123948-87-8, Topotecan 125317-39-7, Navelbine
154361-50-9, Capecitabine 183319-69-9, Tarceva 184475-35-2, Iressa
192185-68-5, R 115777 193275-84-2, SCH66336 195987-41-8, BMS 214662
220127-57-1, Gleevec 253863-00-2, L778123
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(anticancer agent, combination therapy; preparation of pyrazolo[1,5-a]pyrimidines as cyclin dependent kinase inhibitors and anticancer agents)

IT **84449-90-1**, Raloxifene
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(anticancer agent, combination therapy; preparation of pyrazolo[1,5-a]pyrimidines as cyclin dependent kinase inhibitors and anticancer agents)

RN 84449-90-1 HCAPLUS
CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 3 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:220334 HCAPLUS

DOCUMENT NUMBER: 140:270871
TITLE: Preparation of pyrazolo[1,5-a]pyrimidines as cyclin dependent kinase inhibitors and anticancer agents
INVENTOR(S): Guzi, Timothy J.; Paruch, Kamil; Dwyer, Michael P.; Doll, Ronald J.; Girijavallabhan, Viyyoor Moopil; Dillard, Lawrence W.; Tran, Vinh D.; He, Zhen Min; James, Ray Anthony; Park, Haengsoon
PATENT ASSIGNEE(S): Schering Corporation, USA; Pharmacopeia, Inc.
SOURCE: PCT Int. Appl., 83 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004022559	A1	20040318	WO 2003-US27405	20030903
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NI, NO, NZ, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004102451	A1	20040527	US 2003-654157	20030903
PRIORITY APPLN. INFO.:			US 2002-408030P	P 20020904

OTHER SOURCE(S): MARPAT 140:270871
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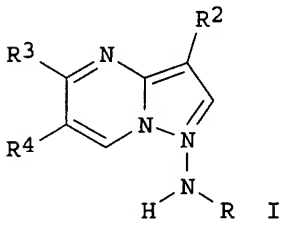


I

AB The title compds. [I; R = (un)substituted heteroaryl; R2 = (un)substituted alkyl, alkynyl, aryl, heteroaryl, alkynylalkyl, CF3, heterocyclylalkyl, alkynylalkyl, cycloalkyl, CO2R4, etc., wherein aryl is optionally substituted; R3 = H, halogen, NR5R6, CO2R4, CONR5R6, each (un)substituted alkyl, alkynyl, cycloalkyl, cycloalkyl, cycloalkylalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, or heteroaryl, etc.; R4 = H, halo, alkyl; R5 = H, alkyl; R6 = H, each (un)substituted alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; or R5 and R6 in the moiety -NR5R6, may be joined together to form an (un)substituted cycloalkyl or heterocyclyl] or pharmaceutically acceptable salts or solvates thereof are prepared In its many embodiments, the present invention also provides methods of preparing such compds., pharmaceutical compns. containing one or more such compds. I, methods of preparing pharmaceutical formulations comprising one or more such compds., and methods of treatment, prevention, inhibition, or amelioration of one

or more diseases associated with cyclin dependent kinase using such compds. I or pharmaceutical compns. The disease associated with cyclin dependent kinase is selected from the group consisting of; (1) cancer of the bladder, breast, colon, kidney, liver, lung, small cell lung cancer, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; (2) leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkitt's lymphoma; (3) acute and chronic myelogenous leukemia, myelodysplastic syndrome and promyelocytic leukemia; (4) fibrosarcoma and rhabdomyosarcoma; (5) astrocytoma, neuroblastoma, glioma and schwannomas; and (6) melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoacanthoma, thyroid follicular cancer and Kaposi's sarcoma.

IC ICM C07D487-04
ICS A61K031-519; A61P025-00; A61P035-00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 7

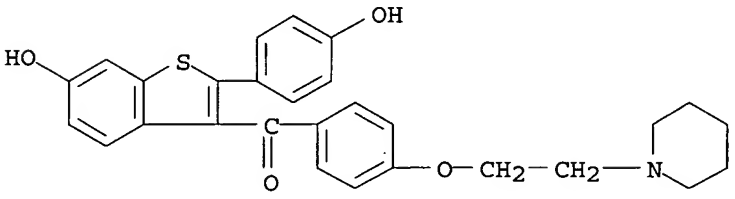
IT Antitumor agents
Bladder, neoplasm
Esophagus, neoplasm
Gallbladder, neoplasm
Hodgkin's disease
Human
Kidney, neoplasm
Leukemia
Liver, neoplasm
Lung, neoplasm
Mammary gland, neoplasm
Melanoma
Myelodysplastic syndromes
Neoplasm
Neuroglia, neoplasm
Ovary, neoplasm
Pancreas, neoplasm
Prostate gland, neoplasm
Skin, neoplasm
Stomach, neoplasm
Thyroid gland, neoplasm
(preparation of pyrazolo[1,5-a]pyrimidines as cyclin **dependent** kinase inhibitors and anticancer agents for treating diseases, in particular various cancers, associated with cyclin **dependent** kinase)

IT 50-07-7, Mitomycin-C 50-18-0, Cyclophosphamide 50-24-8, Prednisolone 50-44-2, 6-Mercaptopurine 50-76-0, Dactinomycin 50-91-9, Floxuridine 51-18-3, Triethylenemelamine 51-21-8, 5-Fluorouracil 51-75-2 52-24-4, Triethylenethiophosphoramide 53-03-2, Prednisone 53-19-0, Mitotane 54-91-1, Pipobroman 55-98-1, Busulfan 56-53-1, Diethylstilbestrol 57-22-7, Vincristine 57-63-6, 17α-Ethynylestradiol 58-05-9, Leucovorin 58-18-4, Methyltestosterone 58-22-0, Testosterone 59-05-2, Methotrexate 66-75-1, Uracil mustard 68-96-2, Hydroxyprogesterone 71-58-9, Medroxyprogesteroneacetate 76-43-7, Fluoxymesterone 83-43-2, Methylprednisolone 124-94-7, Triamcinolone 125-84-8, Aminoglutethimide 127-07-1, Hydroxyurea 147-94-4, Ara-C 148-82-3, Melphalan 154-42-7, 6-Thioguanine 154-93-8, Carmustine 305-03-3, Chlorambucil 521-12-0, Dromostanolone propionate 569-57-3, Chlorotrianisene 595-33-5, Megestrolacetate 645-05-6, Hexamethylmelamine 671-16-9, Procarbazine 865-21-4, Vinblastine 968-93-4, Testolactone 2998-57-4, Estramustine

3778-73-2, Ifosfamide 4342-03-4, Dacarbazine 9015-68-3, L-Asparaginase
10540-29-1, Tamoxifen 11056-06-7, Bleomycin 13010-47-4, Lomustine
13311-84-7, Flutamide 14769-73-4, Levamisole 15663-27-1, Cisplatin
18378-89-7, Mithramycin 18883-66-4, Streptozocin 20830-81-3,
Daunorubicin 23214-92-8, Doxorubicin 25316-40-9, Adriamycin
29767-20-2, Teniposide 33069-62-4, Taxol 33419-42-0, Etoposide
41575-94-4, Carboplatin 51264-14-3, Amsacrine 53643-48-4, Vindesine
53714-56-0, Leuprolide 53910-25-1, Pentostatin 56420-45-2, Epirubicin
58957-92-9, Idarubicin 61825-94-3, Oxaliplatin 65271-80-9,
Mitoxantrone 65807-02-5, Goserelin 75607-67-9, Fludarabine phosphate
82413-20-5, Droloxifene **84449-90-1**, Raloxifene 85622-93-1,
Temozolomide 89778-26-7, Toremifene 95058-81-4, Gemcitabine
97682-44-5, Irinotecan 100286-90-6, CPT-11 114977-28-5, Taxotere
120511-73-1, Anastrozole 123948-87-8, Topotecan 125317-39-7, Navelbine
154361-50-9, Capecitabine 183319-69-9, Tarceva 184475-35-2, Iressa
192185-72-1, Tipifarnib 193275-84-2, Lonafarnib 195987-41-8, BMS
214662 220127-57-1, Gleevec 253863-00-2, L778123
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(anticancer agent, combination therapy; preparation of pyrazolo[1,5-a]pyrimidines as cyclin dependent kinase inhibitors and anticancer agents for treating diseases, in particular various cancers, associated with cyclin dependent kinase)

IT **84449-90-1**, Raloxifene
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(anticancer agent, combination therapy; preparation of pyrazolo[1,5-a]pyrimidines as cyclin dependent kinase inhibitors and anticancer agents for treating diseases, in particular various cancers, associated with cyclin dependent kinase)

RN 84449-90-1 HCAPLUS
CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



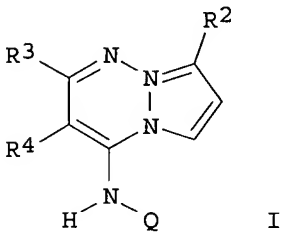
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 4 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2004:220207 HCAPLUS
DOCUMENT NUMBER: 140:270868
TITLE: Preparation of pyrazolo[1,5-a]pyrimidines as cyclin dependent kinase inhibitors and anticancer agents
INVENTOR(S): Guzi, Timothy J.; Paruch, Kamil; Dwyer, Michael P.; Doll, Ronald J.; Girijavallabhan, Viyyoor Moopil; Knutson, Chad; Mckittrick, Brian; Dillard, Lawrence W.; Tran, Vinh D.; He, Zhen Min; James, Ray Anthony; Park, Haengsoon
PATENT ASSIGNEE(S): Schering Corporation, USA; Pharmacopeia, Inc.
SOURCE: PCT Int. Appl., 77 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004022062	A1	20040318	WO 2003-US27564	20030903
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LC, LK, LR, LT, LU, LV, MA, MD, MG, MK, MN, MX, MZ, NI, NO, NZ, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UZ, VC, VN, YU, ZA, ZM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2004102452	A1	20040527	US 2003-654163	20030903
PRIORITY APPLN. INFO.:			US 2002-408182P P	20020904

OTHER SOURCE(S): MARPAT 140:270868
GI



I

AB The title compds. [I; Q = SO2NR6R7, CONR6R7, CO2R7; R2 = (un)substituted alkyl, alkynyl, alkynylalkyl, cycloalkyl, CF3, CO2R6, aryl, arylalkyl, heteroarylalkyl, heterocyclyl, etc., wherein aryl is optionally substituted; R3 = H, halogen, NR5R6, CONR5R6, CO2R4, each (un)substituted alkyl, alkynyl, cycloalkyl, aryl, arylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl, etc.; R4 = H, halo, alkyl; R5 = H, alkyl; R6 = H, each (un)substituted alkyl, aryl, arylalkyl, cycloalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroarylalkyl; R7 = each (un)substituted alkyl, cycloalkyl, aryl, heteroaryl, arylalkyl, or heteroarylalkyl; or R5 and R6 in the moiety -NR5R6, may be joined together to form an (un)substituted cycloalkyl or heterocyclyl] or pharmaceutically acceptable salts or solvates thereof are prepared In its many embodiments, the present invention also provides methods of preparing such compds., pharmaceutical compns. containing one or more such compds. I, methods of preparing pharmaceutical formulations comprising one or more such compds., and methods of treatment, prevention, inhibition, or amelioration of one or more diseases associated with cyclin dependent kinase using such compds. I or pharmaceutical compns. The disease associated with cyclin dependent kinase is selected from the group consisting of; (1) cancer of the bladder, breast, colon, kidney, liver, lung, small cell lung cancer, esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin, including squamous cell carcinoma; (2) leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkitt's lymphoma; (3)

acute and chronic myelogenous leukemia, myelodysplastic syndrome and promyelocytic leukemia; (4) fibrosarcoma and rhabdomyosarcoma; (5) astrocytoma, neuroblastoma, glioma and schwannomas; and (6) melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoacanthoma, thyroid follicular cancer and Kaposi's sarcoma.

IC ICM A61K031-50
ICS A61P035-00; C07D487-04; C07D239-00; C07D231-00

CC 28-16 (Heterocyclic Compounds (More Than One Hetero Atom))
Section cross-reference(s): 1, 7

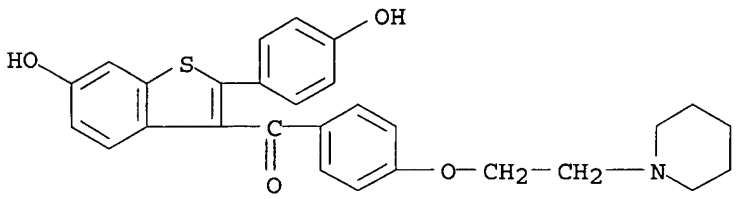
IT Antitumor agents
Bladder, neoplasm
Esophagus, neoplasm
Gallbladder, neoplasm
Hodgkin's disease
Kidney, neoplasm
Leukemia
Liver, neoplasm
Lung, neoplasm
Mammary gland, neoplasm
Melanoma
Myelodysplastic syndromes
Neoplasm
Neuroglia, neoplasm
Ovary, neoplasm
Pancreas, neoplasm
Prostate gland, neoplasm
Skin, neoplasm
Stomach, neoplasm
Thyroid gland, neoplasm
(preparation of pyrazolo[1,5-a]pyrimidines as cyclin **dependent** kinase inhibitors and anticancer agents for treating diseases, in particular various cancers, associated with cyclin **dependent** kinase)

IT 50-07-7, Mitomycin-C 50-18-0, Cyclophosphamide 50-24-8, Prednisolone 50-44-2, 6-Mercaptopurine 50-76-0, Dactinomycin 50-91-9, Floxuridine 51-18-3, Triethylenemelamine 51-21-8, 5-Fluorouracil 51-75-2 52-24-4, Triethylenethiophosphoramide 53-03-2, Prednisone 53-19-0, Mitotane 54-91-1, Pipobroman 55-98-1, Busulfan 56-53-1, Diethylstilbestrol 57-22-7, Vincristine 57-63-6, 17α-Ethynylestradiol 58-05-9, Leucovorin 58-18-4, Methyltestosterone 58-22-0, Testosterone 59-05-2, Methotrexate 66-75-1, Uracil mustard 68-96-2, Hydroxyprogesterone 71-58-9, Medroxyprogesteroneacetate 76-43-7, Fluoxymesterone 83-43-2, Methylprednisolone 124-94-7, Triamcinolone 125-84-8, Aminoglutethimide 127-07-1, Hydroxyurea 147-94-4, Ara-C 148-82-3, Melphalan 154-42-7, 6-Thioguanine 154-93-8, Carmustine 305-03-3, Chlorambucil 521-12-0, Dromostanolone propionate 569-57-3, Chlorotrianisene 595-33-5, Megestrolacetate 645-05-6, Hexamethylmelamine 671-16-9, Procarbazine 865-21-4, Vinblastine 968-93-4, Testolactone 2998-57-4, Estramustine 3778-73-2, Ifosfamide 4342-03-4, Dacarbazine 9015-68-3, L-Asparaginase 10540-29-1, Tamoxifen 11056-06-7, Bleomycin 13010-47-4, Lomustine 13311-84-7, Flutamide 14769-73-4, Levamisole 15663-27-1, Cisplatin 18378-89-7, Mithramycin 18883-66-4, Streptozocin 20830-81-3, Daunorubicin 23214-92-8, Doxorubicin 25316-40-9, Adriamycin 29767-20-2, Teniposide 33069-62-4, Taxol 33419-42-0, Etoposide 41575-94-4, Carboplatin 51264-14-3, Amsacrine 53643-48-4, Vindesine 53714-56-0, Leuprolide 53910-25-1, Pentostatin 56420-45-2, Epirubicin 58957-92-9, Idarubicin 61825-94-3, Oxaliplatin 65271-80-9, Mitoxantrone 65807-02-5, Goserelin 75607-67-9, Fludarabine phosphate

82413-20-5, Droloxifene **84449-90-1**, Raloxifene 85622-93-1, Temozolomide 89778-26-7, Toremifene 95058-81-4, Gemcitabine 97682-44-5, Irinotecan 100286-90-6, CPT-11 114977-28-5, Taxotere 120511-73-1, Anastrozole 123948-87-8, Topotecan 125317-39-7, Navelbine 154361-50-9, Capecitabine 183319-69-9, Tarceva 184475-35-2, Iressa 192185-72-1, Tipifarnib 195987-41-8, BMS 214662 220127-57-1, Gleevec 253863-00-2, L778123 674297-93-9
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(anticancer agent, combination therapy; preparation of pyrazolo[1,5-a]pyrimidines as cyclin dependent kinase inhibitors and anticancer agents for treating diseases, in particular various cancers, associated with cyclin dependent kinase)

IT **84449-90-1**, Raloxifene
RL: **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(anticancer agent, combination therapy; preparation of pyrazolo[1,5-a]pyrimidines as cyclin dependent kinase inhibitors and anticancer agents for treating diseases, in particular various cancers, associated with cyclin dependent kinase)

RN 84449-90-1 HCAPLUS
CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 5 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2003:737607 HCAPLUS
DOCUMENT NUMBER: 139:224420
TITLE: Remedies for sex hormone-dependent disease
INVENTOR(S): Hara, Takahito; Kusaka, Masami
PATENT ASSIGNEE(S): Takeda Chemical Industries, Ltd., Japan
SOURCE: PCT Int. Appl., 79 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003075958	A1	20030918	WO 2003-JP2783	20030310

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES,

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 8 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:728442 HCAPLUS
DOCUMENT NUMBER: 138:248094
TITLE: Raloxifene, a mixed estrogen agonist/antagonist, induces apoptosis in **androgen-independent** human prostate cancer cell lines
AUTHOR(S): Kim, Isaac Yi; Kim, Byung-Chul; Seong, Do Hwan; Lee, Dug Keun; Seo, Jeong-Meen; Hong, Young Jin; Kim, Heung-Tae; Morton, Ronald A.; Kim, Seong-Jin
CORPORATE SOURCE: Laboratory of Cell Regulation and Carcinogenesis, National Cancer Institute, Bethesda, MD, 20892, USA
SOURCE: Cancer Research (2002), 62(18), 5365-5369
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Raloxifene, a selective estrogen receptor (ER) modulator, is a mixed estrogen agonist/antagonist that was shown to prevent osteoporosis and breast cancer in women. Because the prostate contains high levels of ER-β, the present study investigated the effect of raloxifene in 3 well-characterized, **androgen-independent** human prostate cancer cell lines: (a) PC3; (b) PC3M; and (c) DU145. Reverse transcriptase-PCR and Western blot anal. for ER-α and ER-β demonstrated that all 3 cell lines express ER-β, whereas only PC3 and PC3M cells were pos. for ER-α. After the treatment with raloxifene, a dramatic increase in cell death was observed in a dose-dependent manner in the 3 prostate cancer cell lines (10-9 to 10-6 M range). Because the 3 prostate cancer cell lines demonstrated similar morphol. changes after the raloxifene treatment, PC3 (ER-α/ER-β+) and DU145 (ER-β+ only) cells were selected to further characterize the raloxifene-induced cell death. Using the nucleus-specific stain 4',6-diamidino-2-phenylindole, nuclear fragmentation was observed in a time-dependent manner in both cell lines after exposure to 10-6 M raloxifene. Using the terminal deoxynucleotidyl transferase-mediated nick end labeling apoptotic assay, it was demonstrated that the nuclear fragmentation was caused by apoptosis. To investigate the possibility that caspase activation is involved in raloxifene-induced apoptosis, cells were treated with the pan-caspase inhibitor ZVAD. The results demonstrated that the dramatic change in cellular morphol. after treatment with raloxifene was no longer observed when cells were pretreated with ZVAD. Immunoblot demonstrated activation of caspases 8 and 9 in PC3 and DU145 cells, resp. Taken together, these results demonstrate that the mixed estrogen agonist/antagonist, raloxifene, induces apoptosis in **androgen-independent** human prostate cancer cell lines.

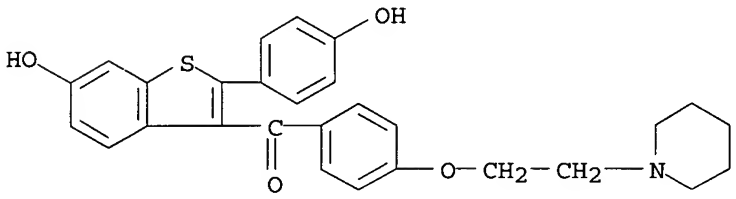
CC 1-6 (Pharmacology)

IT **Prostate gland, neoplasm**
(**androgen-independent**, inhibitor; raloxifene induces apoptosis in **androgen-independent** human prostate cancer)

IT Estrogens
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antiestrogens; raloxifene induces apoptosis in **androgen-independent** human prostate cancer)

IT Estrogen receptors
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(modulator; raloxifene induces apoptosis in **androgen-**

independent human prostate cancer)
IT Antitumor agents
(prostate cancer; raloxifene induces apoptosis in **androgen-independent** human prostate cancer)
IT Apoptosis
Human
(raloxifene induces apoptosis in **androgen-independent** human prostate cancer)
IT **84449-90-1**, Raloxifene
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(raloxifene induces apoptosis in **androgen-independent** human prostate cancer)
IT **84449-90-1**, Raloxifene
RL: **PAC (Pharmacological activity)**; **THU (Therapeutic use)**; BIOL (Biological study); USES (Uses)
(raloxifene induces apoptosis in **androgen-independent** human prostate cancer)
RN 84449-90-1 HCAPLUS
CN Methanone, [6-hydroxy-2-(4-hydroxyphenyl)benzo[b]thien-3-yl][4-[2-(1-piperidinyl)ethoxy]phenyl]- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 9 OF 11 HCAPLUS COPYRIGHT 2005 ACS on STN
ACCESSION NUMBER: 2002:519062 HCAPLUS
DOCUMENT NUMBER: 138:66287
TITLE: Raloxifene, a selective estrogen receptor modulator, induces apoptosis in androgen-responsive human prostate cancer cell line LNCaP through an **androgen-independent** pathway
AUTHOR(S): Kim, Isaac Yi; Seong, Do Hwan; Kim, Byung-Chul; Lee, Dug Keun; Remaley, Alan T.; Leach, Fredrick; Morton, Ronald A.; Kim, Seong-Jin
CORPORATE SOURCE: Laboratory of Cell Regulation and Carcinogenesis, National Cancer Institute, Bethesda, MD, 20892, USA
SOURCE: Cancer Research (2002), 62(13), 3649-3653
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Raloxifene, a selective estrogen receptor (ER) modulator, is a mixed estrogen agonist/antagonist that has been shown to prevent osteoporosis and breast cancer in women. Because the prostate contains a high level of ER-β, the present study investigated the effect of raloxifene in the androgen-sensitive human prostate cancer cell line LNCaP. Previously, it has been demonstrated that LNCaP cells express ER-β but not ER-α and that tamoxifen induces apoptosis in these cells. After

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=> d que l20
L15        31288 SEA FILE=CANCERLIT ABB=ON  PLU=ON  PROSTATIC NEOPLASMS+PFT/CT
L17          452 SEA FILE=CANCERLIT ABB=ON  PLU=ON  L15 AND ANDROGEN DEPENDENT
L18         3763 SEA FILE=CANCERLIT ABB=ON  PLU=ON  PROSTATIC NEOPLASMS+PFT/CT(L
                 )TH
L20           48 SEA FILE=CANCERLIT ABB=ON  PLU=ON  L18 AND L17


=> d l20 bib ab hitind 1-48

L20  ANSWER 1 OF 48  CANCERLIT on STN
AN   2002196213     CANCERLIT
DN   21958723   PubMed ID: 11961667
TI   Transcription-targeted gene therapy for androgen-independent prostate
     cancer.
AU   Martiniello-Wilks Rosetta; Tsatralis Tania; Russell Peter; Brookes Diana
     E; Zandvliet Dorethea; Lockett Linda J; Both Gerald W; Molloy Peter L;
     Russell Pamela J
CS   Oncology Research Centre, Prince of Wales Hospital, Randwick, New South
     Wales 2031, Australia.. r.martiniello@unsw.edu.au
SO   CANCER GENE THERAPY, (2002 May) 9 (5) 443-52.
     Journal code: 9432230. ISSN: 0929-1903.
CY   England: United Kingdom
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   MEDLINE; Priority Journals
OS   MEDLINE 2002224783
EM   200210
ED   Entered STN: 20021115
     Last Updated on STN: 20021115
AB   The Escherichia coli enzyme (purine nucleoside phosphorylase, PNP) gene is
     delivered directly into PC3 tumors by one injection of
     replication-deficient human type-5 adenovirus (Ad5). Expressed PNP
     converts the systemically administered prodrug, 6MPDR, to a toxic purine,
     6MP, causing cell death. We sought to increase the specificity of
     recombinant Ad vectors by controlling PNP expression with the promoter
     region from the androgen-dependent, prostate-specific
     rat probasin (Pb) gene. To increase its activity, the promoter was
     combined with the SV40 enhancer (SVPb). Cell lines were transfected with
     plasmids containing both a reporter gene, under SVPb control, and a
     reference gene cassette to allow normalization of expression levels.
     Plasmids expressed approximately 20-fold more reporter in prostate cancer
     than in other cells, but surprisingly, the SVPb element was both
     androgen-independent and retained substantial prostate specificity.
     Killing by Ad5-SVPb-PNP vector of cell lines cultured with 6MPDR for 6
     days was 5- to 10-fold greater in prostate cancer than in liver or lung
     cells. In vivo, a single intratumoral injection of Ad5-SVPb-PNP (4 x 10(8)
     pfu), followed by 6MPDR administration twice daily for 6 days,
     significantly suppressed the growth of human prostate tumors in nude mice
     and increased their survival compared to control animals. Thus, the
     androgen-independent, prostate-targeting Ad5 vector reduces human prostate
     cancer growth significantly in vitro and in vivo. This first example of an
     androgen-independent vector points the way toward treatment of emerging
     androgen-independent prostate cancer in conjunction with hormone ablation
     therapy at a time when the tumor burden is low.
CT   Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't
      Adenoviridae: GE, genetics
      Androgens: PD, pharmacology
```

*Gene Therapy: MT, methods
Genetic Vectors
Mice
Mice, Nude
Plasmids: ME, metabolism
Prodrugs: PD, pharmacology
***Prostatic Neoplasms: GE, genetics**
***Prostatic Neoplasms: TH, therapy**
Time Factors
Tissue Distribution
*Transcription, Genetic
Transfection
Tumor Cells, Cultured
CN 0 (Androgens); 0 (Genetic Vectors); 0 (Plasmids); 0 (Prodrugs)

L20 ANSWER 2 OF 48 CANCERLIT on STN
AN 2002189110 CANCERLIT
DN 22001574 PubMed ID: 12006246
TI Tissue-specific promoters in gene therapy for the treatment of prostate cancer.
AU Shirakawa T; Gotoh A; Wada Y; Kamidono S; Ko S C; Kao C; Gardner T A; Chung L W
CS Department of Urology, Kobe University School of Medicine, Kobe, Japan.. toshiro@kobe-u.ac.jp
SO MOLECULAR UROLOGY, (2000 Summer) 4 (2) 73-82. Ref: 20
Journal code: 9709255. ISSN: 1091-5362.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2002264833
EM 200210
ED Entered STN: 20021115
Last Updated on STN: 20021115
AB Delivery of therapeutic toxic genes to and their expression in tumor cells through the use of tissue-specific promoters could decrease their toxic effect on neighboring normal cells when virus-mediated gene delivery results in their infection. We have demonstrated the utility of two prostate cancer-specific promoters, long PSA and osteocalcin, for tissue-specific toxic gene therapy for prostate cancer. The two promoters were highly active in both **androgen-dependent** and androgen-independent prostate cancer cells. We also introduce the Phase I trial of osteocalcin promoter-based toxic gene therapy for bone metastases of prostate cancer, which is in progress at the University of Virginia.
CT Check Tags: Animal; Human; Male
Acyclovir: TU, therapeutic use
Clinical Trials, Phase I
*Gene Therapy
Neoplasm Metastasis
Osteocalcin: GE, genetics
Osteosarcoma: GE, genetics
Osteosarcoma: TH, therapy
*Promoter Regions (Genetics)
Prostate-Specific Antigen: GE, genetics
***Prostatic Neoplasms: GE, genetics**
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**

RN 104982-03-8 (Osteocalcin); 59277-89-3 (Acyclovir)
CN EC 3.4.21.77 (Prostate-Specific Antigen)

L20 ANSWER 3 OF 48 CANCERLIT on STN
AN 2002177963 CANCERLIT
DN 22146611 PubMed ID: 12134144
TI Visualization of advanced human prostate cancer lesions in living mice by a targeted gene transfer vector and optical imaging.
AU Adams Jason Y; Johnson Mai; Sato Makoto; Berger Frank; Gambhir Sanjiv S; Carey Michael; Iruela-Arispe M Luisa; Wu Lily
CS Department of Urology, David Geffen School of Medicine at UCLA, Los Angeles California 90095, USA.
NC P50 CA86306 (NCI)
R0-1 CA82214 (NCI)
R24 CA92865 (NCI)
SO NATURE MEDICINE, (2002 Aug) 8 (8) 891-7.
Journal code: 9502015. ISSN: 1078-8956.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2002402559
EM 200209
ED Entered STN: 20021018
Last Updated on STN: 20021018
AB Non-invasive imaging and transcriptional targeting can improve the safety of therapeutic approaches in cancer. Here we demonstrate the ability to identify metastases in a human-prostate cancer model, employing a prostate-specific adenovirus vector (AdPSE-BC-luc) and a charge-coupled device-imaging system. AdPSE-BC-luc, which expresses firefly luciferase from an enhanced prostate-specific antigen promoter, restricted expression in the liver but produced robust signals in prostate tumors. In fact, expression was higher in advanced, androgen-independent tumors than in **androgen-dependent** lesions. Repetitive imaging over a three-week period after AdPSE-BC-luc injection into tumor-bearing mice revealed that the virus could locate and illuminate metastases in the lung and spine. Systemic injection of low doses of AdPSE-BC-luc illuminated lung metastasis. These results demonstrate the potential use of a non-invasive imaging modality in therapeutic and diagnostic strategies to manage prostate cancer.
CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
*Diagnostic Imaging
*Gene Transfer Techniques
*Genetic Vectors
Liver: ME, metabolism
Liver: PA, pathology
Luciferase: GE, genetics
Luciferase: ME, metabolism
Mice
Mice, SCID
Mice, Transgenic
Neoplasm Transplantation
Prostate-Specific Antigen: ME, metabolism
Prostatic Neoplasms: GE, genetics
***Prostatic Neoplasms: PA, pathology**
Prostatic Neoplasms: TH, therapy
Recombinant Fusion Proteins: GE, genetics
Recombinant Fusion Proteins: ME, metabolism

Spine: PA, pathology
CN 0 (Genetic Vectors); 0 (Recombinant Fusion Proteins); EC 1.13.12.- (Luciferase); EC 3.4.21.77 (Prostate-Specific Antigen)

L20 ANSWER 4 OF 48 CANCERLIT on STN
AN 2002162052 CANCERLIT
DN 22032765 PubMed ID: 12036918
TI A novel targeting modality to enhance adenoviral replication by vitamin D(3) in androgen-independent human prostate cancer cells and tumors.
AU Hsieh Chia-Ling; Yang Ling; Miao Li; Yeung Fang; Kao Chinghai; Yang Hua; Zhau Haiyen E; Chung Leland W K
CS Department of Urology, Molecular Urology and Therapeutics Program, Emory University School of Medicine, Atlanta, GA 30322, USA.. chsieh2@emory.edu
NC CA 85555 (NCI)
SO CANCER RESEARCH, (2002 Jun 1) 62 (11) 3084-92.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2002296386
EM 200207
ED Entered STN: 20020819
Last Updated on STN: 20020819
AB We report the development of a novel replication-competent adenoviral vector, Ad-hOC-E1, containing a single bidirectional human osteocalcin (hOC) promoter to drive both the early viral E1A and E1B gene. This vector selectively replicated in OC-expressing but not non-OC-expressing cells, with viral replication enhanced at least 10-fold on vitamin D(3) exposure. Both the artificial TATA-box and hOC promoter element in this bidirectional promoter construct were controlled by a common OC regulatory element which selectively activated OC expression in cells. The expression ofE1A and E1B gene by Ad-hOC-E1 can be markedly induced by vitamin D(3). Unlike Ad-sPSA-E1, an adenoviral vector with viral replication controlled by a strong super prostate-specific antigen (sPSA) promoter which only replicates in PSA-expressing cells with androgen receptor (AR), Ad-hOC-E1 retarded the growth of both **androgen-dependent** and androgen-independent prostate cancer cells irrespective of their basal level of AR and PSA expression. A single i.v. administration of 2 x 10(9) plaque-forming units of Ad-hOC-E1 inhibited the growth of previously established s.c. DU145 tumors (an AR- and PSA-negative cell line). Viral replication is highly enhanced by i.p. administration of vitamin D(3). Ultimately, enhancing Ad-hOC-E1 viral replication by vitamin D(3) may be used clinically to treat localized and osseous metastatic prostate cancer in men.
CT Check Tags: Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
Adenoviridae: DE, drug effects
Adenoviridae: GE, genetics
*Adenoviridae: PH, physiology
Adenovirus E1A Proteins: BI, biosynthesis
Adenovirus E1A Proteins: GE, genetics
Adenovirus E1B Proteins: BI, biosynthesis
Adenovirus E1B Proteins: GE, genetics
Cell Division: GE, genetics
*Cholecalciferol: PD, pharmacology
*Gene Therapy: MT, methods
Genetic Vectors: GE, genetics
Osteocalcin: BI, biosynthesis

Osteocalcin: GE, genetics
Prostatic Neoplasms: ME, metabolism
Prostatic Neoplasms: PA, pathology
Prostatic Neoplasms: TH, therapy
***Prostatic Neoplasms: VI, virology**
RNA, Messenger: BI, biosynthesis
RNA, Messenger: GE, genetics
Up-Regulation
*Virus Replication: DE, drug effects
RN 104982-03-8 (Osteocalcin); 67-97-0 (Cholecalciferol)
CN 0 (Adenovirus E1A Proteins); 0 (Adenovirus E1B Proteins); 0 (Genetic Vectors); 0 (RNA, Messenger)

L20 ANSWER 5 OF 48 CANCERLIT on STN
AN 2002158613 CANCERLIT
DN 21892800 PubMed ID: 11895908
TI The association of p21((WAF-1/CIP1)) with progression to androgen-independent prostate cancer.
AU Fizazi Karim; Martinez Luis A; Sikes Charles R; Johnston Dennis A; Stephens L Clifton; McDonnell Timothy J; Logothetis Christopher J; Trapman Jon; Pisters Louis L; Ordonez Nelson G; Troncoso Patricia; Navone Nora M
CS Department of Genitourinary Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030, USA.
NC CA 75499 (NCI)
SO CLINICAL CANCER RESEARCH, (2002 Mar) 8 (3) 775-81.
Journal code: 9502500. ISSN: 1078-0432.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2002178467
EM 200207
ED Entered STN: 20020819
Last Updated on STN: 20020819
AB The molecular events leading to progression toward androgen-independent prostate cancer (AIPC) are not fully understood. The p21((WAF-1/CIP1)) (p21) gene has been identified as a key factor for the regulation of cell growth. The expression of p21 was examined by immunohistochemical studies in 105 prostate cancer samples: (a) 7 of 30 (23%) **androgen-dependent** tumors; and (b) 36 of 75 (48%) androgen-independent tumors stained positive for p21 ($P < 0.02$). No association was found between p21 expression and p53, bcl-2, and the androgen receptor protein expression in bone metastases of patients with AIPC, whereas there was a significant association with a high Ki-67 index ($P < 0.05$). In 4 of 43 (9%) cases, tumors displayed a p53-negative, bcl-2-negative, and p21-positive phenotype. A xenograft mouse model of prostate cancer using the androgen-responsive MDA PCa 2b prostate cancer cell line was used to study p21 expression after androgen deprivation and at relapse. Androgen deprivation reduced p21 expression to undetectable levels after 14 days. Tumor relapse, defining AIPC, was associated with increased expression of p21 to levels comparable with those found before castration. In this model, p21 expression at relapse was also correlated with a high Ki-67 index. In conclusion, p21 expression is associated with the progression to AIPC. A possible explanation involves a paracrine effect of p21 mediated by the release of mitogenic and antiapoptotic factors. Another explanation involves the regulation of p21 expression by the androgen receptor, which also suggests that p21 may have antiapoptotic function in prostate cancer.
CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.

Androgens: PD, pharmacology
Biopsy
Bone Neoplasms: ME, metabolism
Bone Neoplasms: PA, pathology
Bone Neoplasms: SC, secondary
Cyclins: GE, genetics
*Cyclins: ME, metabolism
Disease Progression
*Gene Expression Regulation, Neoplastic: GE, genetics
Immunoenzyme Techniques
Ki-67 Antigen: ME, metabolism
Mice
Mice, Nude
Neoplasm Recurrence, Local: ME, metabolism
Neoplasm Recurrence, Local: PA, pathology
Neoplasm Staging
Neoplasms, Experimental: ME, metabolism
Neoplasms, Experimental: PA, pathology
***Prostatic Neoplasms: ME, metabolism**
Prostatic Neoplasms: PA, pathology
Prostatic Neoplasms: TH, therapy
Protein p53: ME, metabolism
Proto-Oncogene Proteins c-bcl-2: ME, metabolism
CN 0 (Androgens); 0 (Cip1 protein); 0 (Cyclins); 0 (Ki-67 Antigen); 0 (Protein p53); 0 (Proto-Oncogene Proteins c-bcl-2)

L20 ANSWER 6 OF 48 CANCERLIT on STN
AN 2002117191 CANCERLIT
DN 21611904 PubMed ID: 11745692
TI Expression of basal cell keratins in human prostate cancer metastases and cell lines.
AU van Leenders G J; Aalders T W; Hulsbergen-van de Kaa C A; Ruiter D J; Schalken J A
CS Department of Pathology, University Medical Centre St. Radboud, Nijmegen, The Netherlands.. G.vanleenders@pathol.azn.nl
SO JOURNAL OF PATHOLOGY, (2001 Dec) 195 (5) 563-70.
Journal code: 0204634. ISSN: 0022-3417.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2001698431
EM 200202
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB Within normal human prostate epithelium, basal and luminal cells can be discriminated by their expression of keratins (K). While basal cells express K5/14, luminal cells show expression of K8/18 and an intermediate cell population can be identified by co-expression of K5/18. Prostate cancer is predominantly composed of luminal and neuroendocrine cells, while a minority of cells have a basal phenotype. In order to distinguish between basal and intermediate cells, and to assess the effects of androgen deprivation on prostate cancer, 56 human prostate cancer metastases and three cancer cell lines were characterized using antibodies to K5, K14, K18, and the neuroendocrine marker chromogranin A (ChA). The staining was performed on paraffin tissue and visualized by the avidin-biotin-peroxidase complex method. Protein expression was quantified as the number of positive cells in 20 high power fields (HPF; 400x). Keratin expression in the prostate cancer cell lines LNCaP, DU145, and PC3

was analysed by immunofluorescence with triple staining and confocal laser scanning microscopy. Prostate cancer metastases were consistently positive for K18 and negative for K14, irrespective of hormonal therapy. K5 expression was displayed in 28.9% of the tumours without treatment, in 75% after androgen deprivation, and in 57.1% of hormone-escaped prostate carcinomas. After androgen deprivation, the number of K5-expressing cells increased significantly. While **androgen-dependent** prostate cancer showed a median of 0 cells/20 HPF (range 0-50), regressed tumours displayed 22.5 (range 0-65) and hormone-escaped tumours 7.5 (range 0-361) positive cells/20 HPF. Expression of ChA was observed in 47.4% of the **androgen-dependent** tumours. The number of neuroendocrine cells was not significantly affected in regressed or hormone-escaped disease. The **androgen-dependent** cell line LNCaP stained for K18, while the androgen-independent lines DU145 and PC3 both expressed K5 and 18. Expression of K5 in the absence of K14 identifies the existence of an intermediate cell population in prostate carcinoma. Accumulation of intermediate cells in regressed and hormone-escaped prostate cancer indicates that for their survival, these cells are androgen-independent.

CT Check Tags: Human; Male
Adenocarcinoma: ME, metabolism
*Adenocarcinoma: SC, secondary
Adenocarcinoma: TH, therapy
Chromogranins: ME, metabolism
Immunoenzyme Techniques
*Keratin: ME, metabolism
*Neoplasm Proteins: ME, metabolism
***Prostatic Neoplasms: ME, metabolism**
Prostatic Neoplasms: TH, therapy
Tumor Cells, Cultured
*Tumor Markers, Biological: ME, metabolism

RN 68238-35-7 (Keratin)

CN 0 (Chromogranins); 0 (Neoplasm Proteins); 0 (Tumor Markers, Biological); 0 (chromogranin A); 0 (keratin 5)

L20 ANSWER 7 OF 48 CANCERLIT on STN

AN 2002089066 CANCERLIT

DN 21490851 PubMed ID: 11605036

TI Up-regulation of neuroendocrine differentiation in prostate cancer after androgen deprivation therapy, degree and androgen independence.

AU Ito T; Yamamoto S; Ohno Y; Namiki K; Aizawa T; Akiyama A; Tachibana M

CS Department of Urology, Tokyo Medical University, Tokyo, Japan. takaaki-med.ac.jp.

SO ONCOLOGY REPORTS, (2001 Nov-Dec) 8 (6) 1221-4.
Journal code: 9422756. ISSN: 1021-335X.

CY Greece

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS MEDLINE; Priority Journals

OS MEDLINE 2001558294

EM 200112

ED Entered STN: 20020726
Last Updated on STN: 20020726

AB The up-regulation of neuroendocrine (NE) differentiation after hormonal therapy, as well as the relationship between the degree of NE differentiation and androgen independence was investigated. One hundred and thirty-seven whole prostate specimens that were derived from surgery and autopsy (group A: no hormonal therapy, 44 patients; group B: with

hormonal therapy less than 12 months, 25 patients; group C: with hormonal therapy more than 13 months, 68 patients) were studied. Neuroendocrine differentiation was evaluated by immunostaining with chromogranin A. The degree of NE differentiation was evaluated by the percentage area of positive NE cell expression (grade 0, negative; grade 1, 1-33%; grade 2, 34-66%; grade 3, 67-100%). The degree of NE differentiation was compared in androgen-independent and -dependent tumors in group C. Neuroendocrine differentiation was expressed as 31.8% in group A, 44% in group B and 70.5% in group C ($p<0.001$, Chi-squared test). Group C included 20 androgen-independent cases in which 3 cases were grade 0, 2 were grade 1, 6 were grade 2 and 9 were grade 3. Conversely, for **androgen-dependent** cases, there were 16, 16, 11 and 5 cases, respectively. Neuroendocrine cells, whether positive or not, alone was not significantly different ($p=0.124$, Chi-squared test); however, the percentage area of positive NE cell expression was significantly different between the androgen-independent and -dependent tumors ($p=0.0044$, Chi-squared test). Hormonal therapy may play an important role in the up-regulation of NE differentiation. As well as NE cell expression, whether positive or not, the degree of expression should also be observed to evaluate a poor prognosis, tumor progression and androgen independence.

CT Check Tags: Human; Male
*Androgens: ME, metabolism
Antineoplastic Agents, Hormonal: TU, therapeutic use
*Cell Differentiation
Chromogranins: ME, metabolism
Immunoenzyme Techniques
Neoplasms, Hormone-Dependent: ME, metabolism
*Neoplasms, Hormone-Dependent: PA, pathology
Neoplasms, Hormone-Dependent: TH, therapy
*Neurosecretory Systems: CY, cytology
Prognosis
Prostatic Neoplasms: ME, metabolism
***Prostatic Neoplasms: PA, pathology**
Prostatic Neoplasms: TH, therapy

CN 0 (Androgens); 0 (Antineoplastic Agents, Hormonal); 0 (Chromogranins); 0 (chromogranin A)

L20 ANSWER 8 OF 48 CANCERLIT on STN
AN 2002085432 CANCERLIT
DN 21431954 PubMed ID: 11547123
TI Her-2/neu expression in prostate cancer: high level of expression associated with exposure to hormone therapy and androgen independent disease.
AU Shi Y; Brands F H; Chatterjee S; Feng A C; Groshen S; Schewe J; Lieskovsky G; Cote R J
CS Department of Pathology, University of Southern California Keck School of Medicine and Norris Comprehensive Cancer Center, Los Angeles, California 90003, USA.
SO JOURNAL OF UROLOGY, (2001 Oct) 166 (4) 1514-9.
Journal code: 0376374. ISSN: 0022-5347.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Abridged Index Medicus Journals; Priority Journals
OS MEDLINE 2001498341
EM 200112
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB PURPOSE: HER-2/neu is a proto-oncogene that encodes a transmembrane

receptor belonging to the family of epidermal growth factor receptors. Increasing evidences indicates that HER-2/neu may contribute to hormone resistance in prostate cancer. We investigated HER-2/neu expression in primary, **androgen dependent** and advanced androgen independent prostate cancer, and its potential value as a marker of disease progression. MATERIALS AND METHODS: Immunohistochemical testing was performed to investigate HER-2/neu expression in 81 patients with prostate cancer, including 31 with pathological stage C disease treated with radical prostatectomy without preoperative androgen ablation therapy (untreated group), 30 with pathological stage C disease treated before surgery with androgen ablation therapy (treated group) and 20 with advanced androgen independent prostate cancer (androgen independent group). Tumors were classified based on the percent of tumor cells showing HER-2/neu membrane immunoreactivity as low (50% or less) and high (50% or greater) expression. RESULTS: Of the 31 prostate tumors in the untreated group 9 (29%) showed high HER-2/neu expression versus 15 of 30 (50%) in the treated and 17 of 20 (85%) in the androgen independent groups. The difference in HER-2/neu expression was significant in the untreated and androgen independent ($p < 0.001$) and in the treated and androgen independent ($p = 0.016$) groups. There was a significant association of Gleason score with HER-2/neu expression in the untreated group ($p = 0.038$) but not in the treated group. No association was found of tumor substage with HER-2/neu expression. In the untreated group patients with tumors showing high HER-2/neu expression had a decreased survival rate ($p = 0.044$). CONCLUSIONS: High HER-2/neu expression is highly associated with exposure to hormone therapy and androgen independence. It may contribute to androgen independence in prostate cancer and identify patients with prostate cancer more likely to have disease progression, particularly those not exposed to previous hormone therapy.

CT Check Tags: Human; Male; Support, Non-U.S. Gov't
Aged
*Antineoplastic Agents, Hormonal: TU, therapeutic use
*Diethylstilbestrol: TU, therapeutic use
*Gene Expression Regulation, Neoplastic: GE, genetics
*Genes, erbB-2: GE, genetics
Middle Age
Neoplasm Recurrence, Local: EP, epidemiology
*Orchiectomy
***Prostatic Neoplasms: GE, genetics**
Prostatic Neoplasms: MO, mortality
***Prostatic Neoplasms: TH, therapy**
Survival Rate

RN 56-53-1 (Diethylstilbestrol)
CN 0 (Antineoplastic Agents, Hormonal)

L20 ANSWER 9 OF 48 CANCERLIT on STN
AN 2002080431 CANCERLIT
DN 21523820 PubMed ID: 11668475
TI Peptidylglycine alpha-amidating monooxygenase- and proadrenomedullin-derived peptide-associated neuroendocrine differentiation are induced by androgen deprivation in the neoplastic prostate.
AU Jimenez N; Jongsma J; Calvo A; van der Kwast T H; Treston A M; Cuttitta F; Schroder F H; Montuenga L M; van Steenbrugge G J
CS Department of Histology and Pathology, University of Navarra, 31080 Pamplona, Spain.. njimenez@unav.es
SO INTERNATIONAL JOURNAL OF CANCER, (2001 Oct 1) 94 (1) 28-34. Journal code: 0042124. ISSN: 0020-7136.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2001563753
EM 200111
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB Most PCs show NE differentiation. Several studies have tried to correlate NE expression with disease status, but the reported findings have been contradictory. Prostatic NE cells synthesize peptides with a wide spectrum of potential functions. Some of these active peptides, such as PAMP, are amidated. PAM is the only carboxy-terminal peptide-amidating enzyme identified. We studied expression of PAMP and PAM in normal prostate and prostatic tumors (clinical specimens and human xenograft models) with or without prior androgen-deprivation therapy and found a wide distribution of both molecules in NE subpopulations of all kinds. Although the correlation of either marker to tumor grade, clinical progression or disease prognosis did not reach statistical significance, PAMP- or PAM-immunoreactive cells were induced after androgen-blockade therapy. In the PC-310 and PC-295 **androgen-dependent** models, PAMP or PAM NE differentiation was induced after castration in different ways, being higher in PC-310, which might explain its long-term survival after androgen deprivation. We show induction of expression of 2 new NE markers in clinical specimens and xenografted PC after endocrine therapy.
CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't
*Androgen Antagonists: TU, therapeutic use
Cell Differentiation
*Hydroxylases: AN, analysis
Immunohistochemistry
Mice
*Multienzyme Complexes: AN, analysis
Neoplasm Transplantation
*Neurosecretory Systems: CY, cytology
*Peptide Fragments: AN, analysis
*Prostate: CH, chemistry
***Prostatic Neoplasms: CH, chemistry**
Prostatic Neoplasms: TH, therapy
*Proteins: AN, analysis
Transplantation, Heterologous
CN 0 (Androgen Antagonists); 0 (Multienzyme Complexes); 0 (Peptide Fragments); 0 (Proteins); 0 (proadrenomedullin (1-20)); EC 1.14. (Hydroxylases); EC 1.14.17.3 (peptidylglycine monooxygenase)

L20 ANSWER 10 OF 48 CANCERLIT on STN
AN 2002070842 CANCERLIT
DN 21381055 PubMed ID: 11488070
TI HER2 protein expression and gene amplification in androgen-independent prostate cancer.
AU Reese D M; Small E J; Magrane G; Waldman F M; Chew K; Sudilovsky D
CS Urologic Oncology Program, Division of Hematology-Oncology, Comprehensive Cancer Center, University of California, 2356 Sutter St, 5th Floor, San Francisco, CA 94115, USA.
SO AMERICAN JOURNAL OF CLINICAL PATHOLOGY, (2001 Aug) 116 (2) 234-9. Journal code: 0370470. ISSN: 0002-9173.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Abridged Index Medicus Journals; Priority Journals
OS MEDLINE 2001442751

EM 200108
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB The role of the HER2 receptor remains uncertain in the pathogenesis and progression of human prostate cancer. Previous studies have reported widely divergent rates for HER2 expression in primary prostate tumors, probably owing to significant methodologic differences in the studies. Few data exist about the frequency of HER2 protein overexpression and gene amplification in androgen-independent prostate cancer (AIPC), although recent xenograft models suggest HER2 expression may be up-regulated in the transition from **androgen-dependent** to androgen-independent disease. We studied the role of HER2 protein in AIPC by immunohistochemical and fluorescence in situ hybridization (FISH) analyses on AIPC specimens using well-characterized and validated reagents. Fourteen (36%) of 39 specimens expressed HER2; however, only 2 (5%) had moderate (2+) expression, and 2 (5%) had high-level (3+) expression. Two (6%) of 36 specimens had gene amplification by FISH. These data suggest that HER2 protein overexpression and gene amplification are relatively uncommon in AIPC.
CT Check Tags: Human; Male; Support, Non-U.S. Gov't
Adenoma: CH, chemistry
Adenoma: PA, pathology
Adenoma: TH, therapy
Adult
Aged
Aged, 80 and over
Androgen Antagonists: TU, therapeutic use
*Androgens: PD, pharmacology
Antibodies, Monoclonal
Biopsy
Bone Neoplasms: CH, chemistry
Bone Neoplasms: SC, secondary
*Gene Amplification
*Gene Expression
Immunoenzyme Techniques
In Situ Hybridization, Fluorescence
Lymphatic Metastasis
Middle Age
Neoplasm Metastasis
Neoplasm Recurrence, Local
Prostatectomy
***Prostatic Neoplasms: CH, chemistry**
Prostatic Neoplasms: PA, pathology
Prostatic Neoplasms: TH, therapy
*Receptor, erbB-2: AN, analysis
*Receptor, erbB-2: GE, genetics
CN 0 (Androgen Antagonists); 0 (Androgens); 0 (Antibodies, Monoclonal); EC 2.7.11.- (Receptor, erbB-2)

L20 ANSWER 11 OF 48 CANCERLIT on STN
AN 2002065788 CANCERLIT
DN 21336417 PubMed ID: 11442654
TI Novel therapeutic strategy for advanced prostate cancer using antisense oligodeoxynucleotides targeting anti-apoptotic genes upregulated after androgen withdrawal to delay androgen-independent progression and enhance chemosensitivity.
AU Miyake H; Hara I; Kamidono S; Gleave M E
CS The Prostate Center, Vancouver General Hospital, Vancouver, Canada.. hideakimiyake@hotmail.com

SO INTERNATIONAL JOURNAL OF UROLOGY, (2001 Jul) 8 (7) 337-49. Ref: 61
Journal code: 9440237. ISSN: 0919-8172.
CY Australia
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2001388936
EM 200110
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB Progression to androgen-independence remains the main obstacle to improving survival for patients with advanced prostate cancer. In this review, findings are summarized that have recently been demonstrated to establish novel therapeutic strategy targeting several genes playing functionally important roles after androgen withdrawal and during androgen-independent progression. The authors initially characterized changes in gene expression after androgen withdrawal in the **androgen-dependent** Shionogi and LNCaP tumor models using cDNA arrays. Based on these results, they focused on genes highly upregulated after androgen ablation (i.e. bcl-2, bcl-xL, TR.PM-2, IGFBP-5), which have anti-apoptotic or mitogenic activities, and thereby confer a resistance to androgen withdrawal as well as cytotoxic chemotherapy. The authors further demonstrated the efficacy of an antisense oligodeoxynucleotide (ODN) strategy for patients with advanced prostate cancer through the inhibition of target gene expression, resulting in a delay in the progression to androgen-independence by enhancing apoptotic cell death induced by androgen ablation and chemotherapy. The authors also showed the effectiveness of combined antisense ODN therapy and cytotoxic chemotherapy by achieving additive or synergistic effects. These findings provide a basic significance for the design of clinical studies using antisense ODN either alone or in combination with chemotherapeutic agents in patients with advanced prostate cancer.
CT Check Tags: Human; Male
*Androgens: PH, physiology
*Apoptosis: GE, genetics
Drug Resistance, Neoplasm
*Gene Therapy: MT, methods
Oligodeoxyribonucleotides, Antisense: TU, therapeutic use
Orchiectomy
***Prostatic Neoplasms: TH, therapy**
CN 0 (Androgens); 0 (Oligodeoxyribonucleotides, Antisense)

L20 ANSWER 12 OF 48 CANCERLIT on STN
AN 2001139047 CANCERLIT
DN 21139047 PubMed ID: 11245419
TI Coexpression of the partial androgen receptor enhances the efficacy of prostate-specific antigen promoter-driven suicide gene therapy for prostate cancer cells at low testosterone concentrations.
AU Suzuki S; Tadakuma T; Asano T; Hayakawa M
CS Department of Urology, National Defence Medical College, Tokorozawa, Saitama, Japan.
SO CANCER RESEARCH, (2001 Feb 15) 61 (4) 1276-9.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English

FS MEDLINE; Priority Journals
OS MEDLINE 2001184169
EM 200103
ED Entered STN: 20010515
Last Updated on STN: 20010515
AB The prostate specific antigen (PSA) promoter/enhancer has been clearly demonstrated to be tissue specific, and has been applied to prostate-specific gene therapy. However, the transcription of the PSA gene is strictly **androgen dependent**, and its promoter activity is very weak at low concentrations of testosterone, which are generally observed in prostatic cancer patients treated with androgen deprivation. In this study, we used a partial androgen receptor (ARf) containing amino acids 232-429 and 481-657 to transactivate the PSA gene without androgens. We made two expression vectors, ARfPPLUC and ARfPPTK. They contained ARf cDNA driven by cytomegalovirus promoter and cDNAs of either firefly luciferase (LUC) or herpes simplex virus thymidine kinase (TK) driven by PSA promoter/enhancer (PP). The expressed ARf enhanced the PP activity by about 110-fold in the PSA-producing prostate cancer cell line, LNCaP, under low testosterone concentrations. Moreover, in a PSA-nonproducing prostate cancer cell line, DU145, ARf also enhanced the PP activity by about 60-fold in an androgen-independent manner. In a growth inhibition assay, ARfPPTK treated with ganciclovir was found to inhibit the cell growth of LNCaP cells much more effectively than PPTK. Furthermore, in contrast to PPTK, ARfPPTK also had an inhibitory effect on DU145 cells. This system is thus considered to provide a useful therapeutic option in patients with prostate cancer who are receiving hormonal therapy.
CT Check Tags: Human; Male
Cell Division: GE, genetics
Cloning, Molecular
DNA, Complementary: GE, genetics
Ganciclovir: AD, administration & dosage
*Gene Therapy: MT, methods
Genetic Vectors: GE, genetics
Peptide Fragments: BI, biosynthesis
Peptide Fragments: GE, genetics
Peptide Fragments: PH, physiology
Plasmids: GE, genetics
*Promoter Regions (Genetics)
*Prostate-Specific Antigen: GE, genetics
Prostatic Neoplasms: GE, genetics
Prostatic Neoplasms: ME, metabolism
***Prostatic Neoplasms: TH, therapy**
Receptors, Androgen: BI, biosynthesis
Receptors, Androgen: GE, genetics
*Receptors, Androgen: PH, physiology
*Testosterone: ME, metabolism
Thymidine Kinase: GE, genetics
Thymidine Kinase: ME, metabolism
Trans-Activation (Genetics)
Transfection
Tumor Cells, Cultured
RN 57-85-2 (Testosterone); 82410-32-0 (Ganciclovir)
CN 0 (DNA, Complementary); 0 (Genetic Vectors); 0 (Peptide Fragments); 0 (Plasmids); 0 (Receptors, Androgen); EC 2.7.1.21 (Thymidine Kinase); EC 3.4.21.77 (Prostate-Specific Antigen)

L20 ANSWER 13 OF 48 CANCERLIT on STN
AN 2001107430 CANCERLIT

DN 21107430 PubMed ID: 11170149
TI A monoclonal antibody cytolytic to androgen independent DU145 and PC3 human prostatic carcinoma cells.
AU Talwar G P; Gupta R; Gupta S K; Malhotra R; Khanna R; Mitra D K; Sehgal S; Minz R; Kumar A
CS Talwar Research Foundation, E-6, Neb Valley, Neb Serai, New Delhi, 110 068, India.. talwar37@hotmail.com
SO PROSTATE, (2001 Feb 15) 46 (3) 207-13.
Journal code: 8101368. ISSN: 0270-4137.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2001150037
EM 200103
ED Entered STN: 20010515
Last Updated on STN: 20010515
AB BACKGROUND: While a range of therapeutic products is available for **androgen-dependent** prostatic cancer, no specific intervention modality exists for androgen-independent prostatic cancer. The objective of this research was to explore whether epitopes exist on androgen-independent prostatic DU145 cancer cells, which could be susceptible to cytotoxic action of specific antibodies. METHODS: Hybrid cell clones were developed by immunization of mice with DU145 cells and tested for immunoreactivity by solid phase EIA and cytotoxicity in vitro on DU145 in the presence of the complement, employing colorimetric quantitation by MTS (3- (4-, 5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-(4-sulfophenyl)-2H-tetrazolium). Binding and cytotoxicity studies were also carried out by flow-cytometry. RESULTS: Of 15 stabilized clones immunoreactive with DU145 cells, one monoclonal antibody (mAb 730) manifested cytotoxicity on DU145 cells. Approximately 80% of cells in the DU145 cell line were susceptible to lysis with this antibody at saturating levels. This figure corresponded quantitatively to the number of cells binding with this antibody as determined by Flow-cytometry. Staining with ethidium monoazide bromide (EMA) showed that the cell binding the antibody was also the one killed by the antibody in the presence of the complement. MAb 730 was also cytotoxic to PC3, another androgen-independent human prostatic cancer cell line. This antibody is devoid of classical autoantibody reactivities and does not react with normal human liver, thyroid, kidney, pancreas, and adrenal tissues, as determined by immunofluorescence. Also, it shows negative immuno-reactivity to benign glandular tissue but is observed to positively react with neoplastic prostate tissue. CONCLUSIONS: Epitopes exist on androgen-independent prostatic cancer cells that are susceptible to cytolysis by monoclonal antibodies and these could be investigated for potential immunotherapy.

CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't
Antibodies, Monoclonal: IM, immunology
*Antibodies, Monoclonal: TO, toxicity
Antibody-Dependent Cell Cytotoxicity: IM, immunology
*Carcinoma: IM, immunology
*Carcinoma: TH, therapy
Cell Fusion
Complement: IM, immunology
Dose-Response Relationship, Immunologic
Hybrid Cells: IM, immunology
Hybrid Cells: SE, secretion
Immunoenzyme Techniques

Immunohistochemistry
Mice
Neoplasms, Hormone-Dependent: IM, immunology
Neoplasms, Hormone-Dependent: TH, therapy
Prostate-Specific Antigen: IM, immunology
***Prostatic Neoplasms: IM, immunology**
***Prostatic Neoplasms: TH, therapy**
Spleen: CY, cytology
Spleen: IM, immunology
Tooth, Supernumerary
Tumor Cells, Cultured
RN 9007-36-7 (Complement)
CN 0 (Antibodies, Monoclonal); EC 3.4.21.77 (Prostate-Specific Antigen)

L20 ANSWER 14 OF 48 CANCERLIT on STN
AN 2000383423 CANCERLIT
DN 20383423 PubMed ID: 10928288
TI Apoptosis in prostate carcinogenesis. A growth regulator and a therapeutic target.
AU Bruckheimer E M; Kyprianou N
CS Department of Molecular Biology and Cancer Center, University of Maryland School of Medicine, Baltimore 21201, USA.
NC R01 DK 53525-01 (NIDDK)
SO CELL AND TISSUE RESEARCH, (2000 Jul) 301 (1) 153-62. Ref: 120
Journal code: 0417625. ISSN: 0302-766X.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2001040685
EM 200012
ED Entered STN: 20010423
Last Updated on STN: 20010423
AB Development of effective therapeutic modalities for the treatment of human cancer relies heavily upon understanding the molecular alterations that result in initiation and progression of the tumorigenic process. Many of the molecular changes identified in human prostate tumorigenesis so far play key roles in apoptosis regulation. Apoptosis represents a universal and exquisitely efficient cellular suicide pathway. Since the therapeutic goal is to trigger tumor-selective apoptotic cell death (without clinically significant effects on the host), elucidation of the mechanisms underlying apoptosis deregulation will lead to the identification of specific cellular components for targeting therapeutic interventions. As our understanding of its vital role in the development and growth of the prostate gland has expanded, numerous genes that encode apoptotic regulators have been identified that are severely impaired in prostate cancer cells. In addition, the expression of apoptotic modulators within prostatic tumors appears to correlate with tumor sensitivity to traditional therapies such as hormonal ablation and radiotherapy. No strict correlation between apoptosis induction and a patient's long-term prognosis has emerged, perhaps due to the fact that the ability to achieve initial remission alone does not adequately predict long-term outcome. This review will encompass the known molecular changes intimately involved in the apoptotic pathway which have potential prognostic value in disease progression, as well as therapeutic significance in the enhancement of the apoptotic response to novel and established treatment strategies for the treatment of **androgen-dependent** and

androgen-independent prostatic tumors. The main focus will be on the role of the transforming growth factor-beta (TGF-beta) signaling pathway, bcl-2 and the bcl-2 family members, the caspase cascade (apoptosis executioners), and the Fas pathway in induction and regulation of apoptosis following therapeutic stimuli for the management of advanced prostate cancer.

CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Antigens, CD95: PH, physiology
*Apoptosis: PH, physiology
Caspases: ME, metabolism
Caspases: PH, physiology
Cell Cycle
Mice
Prostatic Neoplasms: ME, metabolism
***Prostatic Neoplasms: PP, physiopathology**
***Prostatic Neoplasms: TH, therapy**
Proto-Oncogene Proteins c-bcl-2: PH, physiology
Transforming Growth Factor beta: PH, physiology

CN 0 (Antigens, CD95); 0 (Proto-Oncogene Proteins c-bcl-2); 0 (Transforming Growth Factor beta); 0 (transforming growth factor beta1); EC 3.4.22.- (Caspases)

L20 ANSWER 15 OF 48 CANCERLIT on STN
AN 2000358892 CANCERLIT
DN 20358892 PubMed ID: 10903068
TI Transforming growth factor-beta1 and prostate cancer.
AU Wikstrom P; Bergh A; Damber J E
CS Department of Surgical and Perioperative Sciences, Umea University, Sweden.
SO SCANDINAVIAN JOURNAL OF UROLOGY AND NEPHROLOGY, (2000 Apr) 34 (2) 85-94. Ref: 104
Journal code: 0114501. ISSN: 0036-5599.
CY Sweden
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2001068215
EM 200012
ED Entered STN: 20010423
Last Updated on STN: 20010423
AB Transforming growth factor-beta1 (TGF-beta1) is an important regulator of the normal and malignant prostate. In the non-malignant prostate, TGF-beta1 stimulates cell differentiation, inhibits epithelial cell proliferation and induces epithelial cell death. TGF-beta1 is secreted into semen and here it is an important immunosuppressive factor. Prostate cancer cells express high levels of TGF-beta1 and it seems to enhance prostate cancer growth and metastasis by stimulating angiogenesis and by inhibiting immune responses directed against tumour cells. Prostate cancer cells frequently lose their TGF-beta receptors and acquire resistance to the anti-proliferative and pro-apoptotic effects of TGF-beta1. Accordingly, high expression of TGF-beta1 and loss of TGF-beta receptor expression have been associated with a particularly bad prognosis in human prostate cancer patients. TGF-beta1 also seems to be a mediator of castration-induced apoptosis in **androgen dependent** normal and malignant prostate epithelial cells. The ability of some prostate tumours to avoid castration-induced apoptosis is however not

simply due to loss of TGF-beta receptor type I or II expression in the tumour cells, but may also be related to an inability of these cells to up-regulate TGF-beta receptor levels in response to castration or possibly due to defects downstream of the receptors. Short-term therapy-induced changes in the TGF-beta system in prostate tumours can probably be used to predict the long-term response to androgen ablation treatment. Further investigations into the TGF-beta system in the prostate are, however, needed to elucidate how alterations in this system affect the behaviour of prostate tumours, and if this system can be manipulated for therapeutical purposes.

CT Check Tags: Human; Male; Support, Non-U.S. Gov't
Disease Progression
Gene Expression Regulation, Neoplastic
Orchiectomy
Prognosis
Prostatic Neoplasms: GE, genetics
***Prostatic Neoplasms: PA, pathology**
Prostatic Neoplasms: TH, therapy
RNA, Messenger: BI, biosynthesis
Receptors, Transforming Growth Factor beta: GE, genetics
*Transforming Growth Factor beta: PH, physiology
Treatment Outcome

CN 0 (RNA, Messenger); 0 (Receptors, Transforming Growth Factor beta); 0 (Transforming Growth Factor beta)

L20 ANSWER 16 OF 48 CANCERLIT on STN
AN 2000354708 CANCERLIT
DN 20354708 PubMed ID: 10898343
TI Establishment of human prostate carcinoma skeletal metastasis models.
AU Zhau H E; Li C L; Chung L W
CS Department of Urology, University of Virginia Health System, Charlottesville 22908, USA.
NC CA6334 (NCI)
CA76620 (NCI)
SO CANCER, (2000 Jun 15) 88 (12 Suppl) 2995-3001. Ref: 42
Journal code: 0374236. ISSN: 0008-543X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Abridged Index Medicus Journals; Priority Journals
OS MEDLINE 2000354708
EM 200007
ED Entered STN: 20000811
Last Updated on STN: 20000811
AB BACKGROUND: Prostate carcinoma progression from an **androgen dependent** (AD) state to an androgen independent (AI) state occurs clinically in patients who undergo hormonal therapy. In their laboratory, the authors developed two human prostate carcinoma skeletal metastasis models, the LNCaP progression model and the ARCaP model, to investigate phenotypic and genotypic changes of prostate carcinoma cells during disease progression and to understand molecular pathways for potential therapeutic targeting. METHODS: LNCaP or ARCaP cells were inoculated in athymic mice and were exposed to selective hormonal conditions both in vivo and in vitro. The effects of various hormonal treatment regimens on tumor volumes and distant metastasis and the effects of bone stromal cells on prostate specific antigen (PSA) expression by prostate carcinoma cells were evaluated. RESULTS: The authors propose that prostate carcinoma

progression from the AD state to the AI state assumes three AI phenotypes: AI that remains androgen responsive, AI that is unresponsive to androgen stimulation, and AI that is suppressed by or hypersensitive to androgen. AI prostate carcinoma cells interacted reciprocally with osteoblasts to produce enhanced tumor growth and osteoblastic reaction when they are deposited in bone. Bone stromal cell conditioned media stimulated prostate carcinoma cell growth and suppressed its PSA expression, as also evidenced by androgen receptor-mediated transactivation of PSA promoter reporter activity. Conditioned media obtained from prostate carcinoma cells also stimulated osteoblastic cell growth in vitro. A novel gene therapy strategy is being developed to target prostatic tumor epithelium and its supporting stroma using tissue specific and tumor-restricted, promoter-directed toxic gene expression in both cellular compartments. In addition, new strategies are being designed to target the tumor endothelial system in the stroma and tumor cell-extracellular matrix interaction mediated by isotype specific integrins. CONCLUSIONS: Prostate carcinoma skeletal metastasis models may prove useful in developing a new targeting strategy for the prevention and treatment of patients with prostate carcinoma.

CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
*Bone Neoplasms: SC, secondary
*Disease Models, Animal
Mice
***Prostatic Neoplasms: PA, pathology**
Prostatic Neoplasms: TH, therapy

L20 ANSWER 17 OF 48 CANCERLIT on STN
AN 2000223938 CANCERLIT
DN 20223938 PubMed ID: 10759680
TI Adenovirus-mediated suicide-gene therapy using the herpes simplex virus thymidine kinase gene in cell and animal models of human prostate cancer: changes in tumour cell proliferative activity.
AU Cheon J; Kim H K; Moon D G; Yoon D K; Cho J H; Koh S K
CS Department of Urology and Pathology, Korea University Hospital, Seoul, Korea.. jcheon@ns.kumc.or.kr
SO BJU INTERNATIONAL, (2000 Apr) 85 (6) 759-66.
Journal code: 100886721. ISSN: 1464-4096.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2000223938
EM 200005
ED Entered STN: 20000622
Last Updated on STN: 20000622
AB OBJECTIVES: To determine the feasibility and efficacy of suicide-gene therapy using adenovirus (Ad)-mediated herpes simplex virus thymidine kinase (HSV-TK) and the prodrug acyclovir, and to evaluate changes in the biological phenotype for tumour cell proliferative activity after suicide-gene therapy in animal models of human prostate cancer. MATERIALS AND METHODS: Using a replication-defective adenoviral vector (cytomegalovirus, CMV) containing the beta-galactosidase gene (Ad-CMV-beta-gal) as a control and Ad-CMV-TK as the therapeutic vector under the transcriptional control of the CMV promoter, transduction efficiency was assessed in vitro by infecting LNCaP and PC-3 **androgen-dependent** and independent human prostate cancer cells with Ad-CMV-beta-gal, and using X-gal staining. The TK activity in prostate cancer cells infected with Ad-CMV-TK was determined by measuring

TK-mediated [3H]-gancyclovir phosphorylation. The sensitivity of LNCaP and PC-3 cells to Ad-CMV-TK in vitro was determined after infection with the therapeutic vector with or without acyclovir. The inhibition of PC-3 tumour growth in vivo induced by the Ad-CMV-TK/acyclovir suicide-gene system was assessed in separate and controlled experiments using human prostate cancer mouse models. Ki-67 proliferative antigen and proliferating cell nuclear antigen (PCNA), both useful proliferative indices, were evaluated using immunohistochemical staining (MIB-1 monoclonal antibody and monoclonal anti-PCNA antibody) in formalin-fixed, paraffin-embedded tissues from gene therapy-treated and control animals. RESULTS: The mean TK activity was significantly higher in LNCaP and PC-3 cells infected with Ad-CMV-TK than in cells infected with Ad-CMV-beta-gal, used as a control ($P < 0.05$). The growth of human prostate cancer cells with Ad-CMV-TK was significantly inhibited by adding acyclovir in vitro ($P < 0.05$). In the in vivo experiments using the PC-3 human prostate cancer mouse model, tumour volume and growth was lower in mice treated with Ad-CMV-TK/acyclovir than in those treated with Ad-CMV-TK only, acyclovir only or untreated (controls) ($P < 0.05$). Histochemical staining of tumour tissues showed that Ad-CMV-TK/acyclovir destroyed PC-3 tumours through tumour cell death and apoptosis, with local lymphatic infiltration. The mean PCNA labelling index in prostate cancer cells of mice treated with Ad-CMV-TK/acyclovir was significantly lower than that in untreated controls ($P < 0.05$, Mann-Whitney U-test). The Ki-67 labelling index in prostate cancer cells of mice treated with Ad-CMV-TK/acyclovir was also lower than that in untreated controls ($P < 0.05$, Student's t-test). Adenovirus-mediated suicide-gene therapy using the HSV-TK gene decreased the proliferative activity of PC-3 human prostatic cancer cells in vivo. CONCLUSIONS: Adenovirus-mediated suicide-gene therapy using an HSV-TK/acyclovir system provided effective therapy in an experimental human prostate cancer mouse model, by significantly inhibiting tumour growth and decreasing the proliferative activity of human prostate cancer cells. Such therapy could be developed as a novel method for treating patients with androgen-independent prostate cancer.

CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't
Antiviral Agents: TU, therapeutic use
Cytomegalovirus: EN, enzymology
*Cytomegalovirus: GE, genetics
Ganciclovir: TU, therapeutic use
Gene Expression
*Gene Therapy: MT, methods
Genetic Vectors: AD, administration & dosage
Mice
***Prostatic Neoplasms: TH, therapy**
*Simplexvirus: EN, enzymology
Statistics, Nonparametric
*Thymidine Kinase: GE, genetics
Tumor Cells, Cultured
beta-Galactosidase: GE, genetics

RN 82410-32-0 (Ganciclovir)

CN 0 (Antiviral Agents); 0 (Genetic Vectors); EC 2.7.1.21 (Thymidine Kinase); EC 3.2.1.23 (beta-Galactosidase)

L20 ANSWER 18 OF 48 CANCERLIT on STN

AN 2000016432 CANCERLIT

DN 20016432 PubMed ID: 10547578

TI Androgen receptor gene amplification increases tissue PSA protein expression in hormone-refractory prostate carcinoma.

AU Koivisto P A; Helin H J

CS Laboratory of Cancer Genetics, Department of Clinical Chemistry, Tampere

University Hospital, P.O. Box 2000, FIN-33521 Tampere, Finland.. blpako@uta.fi
SO JOURNAL OF PATHOLOGY, (1999 Oct) 189 (2) 219-23.
Journal code: 0204634. ISSN: 0022-3417.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2000016432
EM 200003
ED Entered STN: 20000413
Last Updated on STN: 20000413
AB Androgen receptor (AR) gene amplification was analysed by fluorescence in situ hybridization (FISH) from 24 paraffin-embedded prostate carcinoma samples recurring locally during hormonal therapy and prostate-specific antigen (PSA) expression from 15/24 of these samples was studied by immunohistochemistry (IHC). AR gene amplification was detected in 29 per cent (7/24) of the recurrent tumours. Using modified Histoscore (MHS), PSA immunostaining in the AR gene-amplified tumours (133+/-102) was twice as high (p=0.054) as in tumours with no amplification (66+/-79) and a statistically significant (p=0.026) association between AR gene amplification and PSA positivity was found when MHS>/=20 was considered positive for PSA. AR gene copy number was positively correlated with PSA MHS in the AR gene-amplified tumours (r=0.893, p=0.012). Histological grade, Gleason's score, and tumour stage did not differ significantly between patients with and without AR gene amplification. In conclusion, these results indicate that AR gene amplification leads to up-regulation of PSA gene (and possibly other **androgen-dependent** genes), and that patients with AR gene amplification may have elevated serum PSA concentrations without a clear correlation with actual tumour burden.

CT Check Tags: Human; Male
Gene Amplification
Immunoenzyme Techniques
In Situ Hybridization, Fluorescence
*Neoplasm Recurrence, Local: GE, genetics
Neoplasm Recurrence, Local: ME, metabolism
Neoplasm Recurrence, Local: TH, therapy
*Prostate-Specific Antigen: ME, metabolism
***Prostatic Neoplasms: GE, genetics**
Prostatic Neoplasms: ME, metabolism
Prostatic Neoplasms: TH, therapy
*Receptors, Androgen: GE, genetics
Treatment Failure
*Tumor Markers, Biological: ME, metabolism
CN 0 (Receptors, Androgen); 0 (Tumor Markers, Biological); EC 3.4.21.77 (Prostate-Specific Antigen)

L20 ANSWER 19 OF 48 CANCERLIT on STN
AN 1999446868 CANCERLIT
DN 99446868 PubMed ID: 10519379
TI Response of prostate cancer to anti-Her-2/neu antibody in **androgen -dependent** and -independent human xenograft models.
AU Agus D B; Scher H I; Higgins B; Fox W D; Heller G; Fazzari M; Cordon-Cardo C; Golde D W
CS Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.. d-agus@ski.mskcc.org
SO CANCER RESEARCH, (1999 Oct 1) 59 (19) 4761-4.

Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 1999446868
EM 199911
ED Entered STN: 20000221
Last Updated on STN: 20000221
AB Antibody to the Her-2/neu gene product has been shown to inhibit the growth of breast cancer cells overexpressing Her-2/neu and to have clinical utility in treating breast cancer. We studied a recombinant, humanized anti-Her-2/neu antibody (Herceptin) in preclinical models of human prostate cancer. The **androgen-dependent** CWR22 and LNCaP human prostate cancer xenograft models and androgen-independent sublines of CWR22 were used. Her-2/neu staining of the parental, **androgen-dependent**, and androgen-independent CWR22 tumors and LNCaP tumors demonstrated variable Her-2/neu expression. Herceptin was administered i.p. at a dose of 20 mg/kg twice weekly after the xenograft had been established. No effect of Herceptin on tumor growth was observed in any of the androgen-independent tumors; however, significant growth inhibition was observed in both of the **androgen -dependent** xenograft models, CWR22 (68% growth inhibition at the completion of the experiment; P = 0.03 for trajectories of the average tumor volume of the groups) and LNCaP (89% growth inhibition; P = 0.002). There was a significant increase in prostate-specific antigen (PSA) index (ng PSA/ml serum/mm3 tumor) in Herceptin-treated **androgen-dependent** groups compared with control (CWR22, 18-fold relative to pretreatment value versus 1.0-fold, P = 0.0001; LNCaP, 2.35-fold relative to pretreatment value versus 0.6-fold, P = 0.001). When paclitaxel (6.25 mg/kg s.c., five times/week) was given to animals with **androgen-dependent** and -independent tumors, there was growth inhibition in each group. Paclitaxel and Herceptin cotreatment led to greater growth inhibition than was seen for the agents individually. Thus, in these prostate cancer model systems, Herceptin alone has clinical activity only in the **androgen-dependent** tumor and has at least an additive effect on growth, in combination with paclitaxel, in both **androgen-dependent** and androgen-independent tumors. Response to Herceptin did not correlate with the PSA levels, because the PSA index markedly increased in the Herceptin-treated group, whereas it remained constant in the control group. These results suggest the utility of Herceptin in the treatment of human prostate cancer.
CT Check Tags: Animal; Female; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*Antibodies, Monoclonal: TU, therapeutic use
*Antineoplastic Agents: TU, therapeutic use
Immunohistochemistry
Mice
Mice, Nude
Paclitaxel: TU, therapeutic use
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**
*Receptor, erbB-2: IM, immunology
Transplantation, Heterologous
RN 33069-62-4 (Paclitaxel)
CN 0 (Antibodies, Monoclonal); 0 (Antineoplastic Agents); 0 (trastuzumab); EC 2.7.11.- (Receptor, erbB-2)

L20 ANSWER 20 OF 48 CANCERLIT on STN

AN 1999211477 CANCERLIT
DN 99211477 PubMed ID: 10197620
TI Identification of the transcriptional regulatory sequences of human kallikrein 2 and their use in the construction of calydon virus 764, an attenuated replication competent adenovirus for prostate cancer therapy.
AU Yu D C; Sakamoto G T; Henderson D R
CS Calydon, Inc., Sunnyvale, California 94089, USA.
SO CANCER RESEARCH, (1999 Apr 1) 59 (7) 1498-504.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 1999211477; GENBANK-AF113169
EM 199904
ED Entered STN: 19990519
Last Updated on STN: 19990519
AB Human glandular kallikrein (hK2) and prostate-specific antigen (PSA) are related members of the human kallikrein gene family. The genes for hK2 and PSA are expressed predominately in the prostate, are transcriptionally up-regulated by androgens, and share 78% homology. Previously, one functional androgen response element was identified within the proximal promoter (-324 to +33 relative to the cap site) of the hK2 gene. To detect additional upstream regulatory elements, the 12.3 kbp between the PSA gene and 5' to the hK2 gene were amplified by PCR and linked to a promoterless firefly luciferase reporter gene. Transient transfection experiments showed an **androgen-dependent** enhancer, located between -3.4 and -5.2 kb upstream of the transcription start site of the hK2 gene. This hK2 enhancer increased luciferase expression 100-fold in the presence of the testosterone analogue R1881. The hK2 enhancer contains an androgen response element that lost activity when mutated. The hK2 enhancer/promoter demonstrated activity in PSA(+) LNCaP cells whereas the enhancer/promoter was inactive in PSA(-) 293, A549, HBL100, HUH-7, LoVo, MCF-7, OVCAR-3, and PC-3 cells. Insertion of the hK2 enhancer/promoter into adenovirus to drive the E1A genes of adenovirus type 5 (Ad5) created an attenuated replication competent adenovirus variant Calydon virus (CV) 763, which replicates similarly to wild-type adenovirus in prostate tumor cells but is attenuated in nonprostate tumor cells. In addition, CV764, an adenovirus variant containing the previously cloned prostate-specific enhancer (to drive the Ad5 E1A genes) and the hK2 enhancer/promoter (to drive the Ad5 E1B genes) was constructed. CV764 is significantly attenuated and has a high therapeutic index with a cell specificity of 10,000:1 for PSA(+) LNCaP cells, compared to ovarian cancer OVCAR-3 cells and SK-OV-3 cells and PA-1 cells. CV764 is also highly attenuated in primary human microvascular endothelial cells.
CT Check Tags: Human; Male
*Adenoviridae: GE, genetics
Base Sequence
Enhancer Elements (Genetics)
Gene Therapy
*Kallikreins: GE, genetics
Molecular Sequence Data
Organ Specificity
Promoter Regions (Genetics)
***Prostatic Neoplasms: TH, therapy**
Transcription, Genetic
Virus Replication
CN EC 3.4.21.- (Kallikreins)

L20 ANSWER 21 OF 48 CANCERLIT on STN
AN 1998290618 CANCERLIT
DN 98290618 PubMed ID: 9628654
TI Development of prostate-specific antigen promoter-based gene therapy for androgen-independent human prostate cancer.
AU Gotoh A; Ko S C; Shirakawa T; Cheon J; Kao C; Miyamoto T; Gardner T A; Ho L J; Cleutjens C B; Trapman J; Graham F L; Chung L W
CS Department of Urology, Molecular Urology and Therapeutics Program, University of Virginia, Charlottesville 22908, USA.
NC 1R29CA74042-01 (NCI)
SO JOURNAL OF UROLOGY, (1998 Jul) 160 (1) 220-9.
Journal code: 0376374. ISSN: 0022-5347.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Abridged Index Medicus Journals; Priority Journals
OS MEDLINE 1998290618
EM 199807
ED Entered STN: 19980805
Last Updated on STN: 19980805
AB PURPOSE: The goal of this study is to develop a tissue-specific toxic gene therapy utilizing the prostate specific antigen (PSA) promoter for both **androgen-dependent** (AD) and androgen-independent (AI) PSA-secreting prostate cancer cells. Ideally this gene therapy would be effective without the necessity of exposing the target cells to circulating androgens. MATERIALS AND METHODS: An AI subline of LNCaP, an AD PSA-secreting human prostate cancer cell line, C4-2, was used in this study. Castrated mice bearing C4-2 tumors secrete PSA. A transient expression experiment was used to analyze the activity of two PSA promoters, a 5837 bp long PSA promoter and a 642 bp short PSA promoter, in C4-2 cells. A recombinant adenovirus (Ad-PSA-TK) carrying thymidine kinase under control of the long PSA promoter was generated. The tissue-specific activity of Ad-PSA-TK was tested in vitro and in vivo. RESULTS: The long PSA promoter had superior activity over short PSA promoter, and higher activity in C4-2 cells than in LNCaP cells. High activity of Ad-PSA-TK was observed in C4-2 cells in an androgen deprived condition. In vitro, Ad-PSA-TK was further demonstrated to induce marked C4-2 cell-kill by acyclovir in medium containing 5% FBS. No cell-kill was observed in control WH cells (a human bladder cancer cell line). In vivo, Ad-PSA-P-TK with acyclovir significantly inhibited subcutaneous C4-2 tumor growth and PSA production in castrated animals. CONCLUSION: The 5837 bp long PSA promoter was active in the androgen free environment and could be used to target both **androgen-dependent** and independent PSA-producing prostate cancer cells in vitro, and prostate tumors in castrated hosts.
CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Adenoviridae: GE, genetics
*Gene Therapy
Mice
Prostate-Specific Antigen: BI, biosynthesis
*Prostate-Specific Antigen: GE, genetics
Prostatic Neoplasms: ME, metabolism
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**
Recombination, Genetic
Species Specificity
Thymidine Kinase: BI, biosynthesis
Thymidine Kinase: GE, genetics

Transfection
Tumor Cells, Cultured
CN EC 2.7.1.21 (Thymidine Kinase); EC 3.4.21.77 (Prostate-Specific Antigen)

L20 ANSWER 22 OF 48 CANCERLIT on STN
AN 1998266451 CANCERLIT
DN 98266451 PubMed ID: 9605414
TI Effect of the dual 5alpha-reductase inhibitor PNU 157706 on the growth of dunning R3327 prostatic carcinoma in the rat.
AU Zaccheo T; Giudici D; di Salle E
CS Experimental Endocrinology, Research/Oncology, Pharmacia and Upjohn, Nerviano (MI), Italy.. tiziana.zaccheo@eu.pnu.com
SO JOURNAL OF STEROID BIOCHEMISTRY AND MOLECULAR BIOLOGY, (1998 Feb) 64 (3-4) 193-8.
Journal code: 9015483. ISSN: 0960-0760.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 1998266451
EM 199806
ED Entered STN: 19980713
Last Updated on STN: 19980713
AB PNU 157706 [N-(1,1,1,3,3,3-hexafluorophenylpropyl)-3-oxo-4-aza-5alpha-androst-1-ene-17beta-carboxamide] is a novel, potent and selective dual 5alpha-reductase inhibitor. We have investigated its effect on tumor growth, endocrine organ weights and prostatic dihydrotestosterone (DHT) content in rats bearing the **androgen dependent** Dunning R3327 prostatic carcinoma. Animals with tumor diameters of about 1 cm were treated orally for 9 weeks with PNU 157706 (2 and 10 mg/kg/day, 6 days a week) or they were castrated, to check the hormone responsiveness of the tumor. PNU 157706 was effective at both doses tested in reducing tumor growth (53 and 51% inhibition at 2 and 10 mg/kg/day, respectively), while castration caused higher inhibition (82%) of tumor growth. A marked reduction of ventral prostate weight occurred in rats treated with both doses of PNU 157706 (75 and 78%) or castrated (91%). Seminal vesicle weight was also reduced by PNU 157706 administration (56 and 61% inhibition), whereas testes, adrenal, thymus and pituitary weights were not affected. Prostatic DHT content was markedly suppressed (85 and 91%) in PNU 157706 treated rats, compared to 95% suppression caused by castration. These data support a possible role of dual 5alpha-reductase inhibitors in the hormonal therapy of prostatic cancer.
CT Check Tags: Animal; Male
*Androstenes: PD, pharmacology
Antineoplastic Agents: PD, pharmacology
Castration
Cell Division: DE, drug effects
Enzyme Inhibitors: PD, pharmacology
Epididymis: DE, drug effects
Molecular Structure
Organ Weight: DE, drug effects
Prostate: DE, drug effects
***Prostatic Neoplasms: EN, enzymology**
Prostatic Neoplasms: TH, therapy
Rats
Rats, Inbred Strains
Seminal Vesicles: DE, drug effects
Stanolone: AN, analysis
Testis: DE, drug effects

*Testosterone 5-alpha-Reductase: AI, antagonists & inhibitors
RN 521-18-6 (Stanolone)
CN 0 (Androstenes); 0 (Antineoplastic Agents); 0 (Enzyme Inhibitors); 0 (PNU 157706); EC 1.3.99.5 (Testosterone 5-alpha-Reductase)

L20 ANSWER 23 OF 48 CANCERLIT on STN
AN 1998098359 CANCERLIT
DN 98098359 PubMed ID: 9436028.
TI Human prostate cancer progression models and therapeutic intervention.
AU Chung L W; Kao C; Sikes R A; Zhau H E
CS Department of Urology, University of Virginia Health Sciences Center, Charlottesville, USA.
NC RO1 CA64863 (NCI)
SO HINYOKIKA KIYO. ACTA UROLOGICA JAPONICA, (1997 Nov) 43 (11) 815-20. Ref: 12
Journal code: 0421145. ISSN: 0018-1994.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 1998098359
EM 199802
ED Entered STN: 19980417
Last Updated on STN: 19980417
AB Our laboratory has developed two cellular models of human prostate cancer progression. The LNCaP prostate cancer progression model is based upon the well-known cellular interaction between human prostate or bone stromal cells and LNCaP cells in vivo. The marginally tumorigenic LNCaP cells acquired tumorigenic and metastatic potential upon cellular interaction with either prostate or bone fibroblasts. A subline termed C4-2 was observed to grow readily in castrated animals and acquired metastatic potential spreading from the primary tumor site to the lymph node, the seminal vesicles, and the axial skeleton, resulting in an intense osteoblastic reaction. The second model is ARCaP, where prostate cancer cells derived from the ascites fluid of a man with metastatic disease exhibited an Androgen- and estrogen-Repressed Prostate Cancer cell growth and tumor formation in either a hormone-deficient or a castrated environment. However, the growth of either the tumor cells in vitro or the tumors in vivo was suppressed by both estrogen and androgen. While the tumor cells expressed low levels of androgen receptor and prostate-specific antigen (PSA), they were highly metastatic when inoculated orthotopically. Distant metastases to a number of organs were detected, including the liver, lung, kidney, and bone. We have employed a human prostate cancer progression model as a system to study the efficacy of gene therapy. Results of the study show that whereas universal promoters, such as Cytomegalovirus (CMV) and Rous Sarcoma Virus (RSV) promoter-driven tumor suppressors (e.g. p53, p21, and p16), were effective in inhibiting prostate tumor growth, the advantages of driving the expression of therapeutic toxic genes using a tissue-specific promoter prostate-specific antigen (PSA) and a tumor--but not tissue-specific promoter, osteocalcin (OC), are preferred. In the case of the PSA promoter, we can achieve cell-kill in PSA-producing human prostate cancer cells. To circumvent the supporting role of bone stroma for prostate cancer epithelial growth, we have recently developed a novel concept where the expression of therapeutic toxic genes is driven by a tumor--but not a tissue-specific OC promoter. Osteocalcin-thymidine kinase (OC-TK) was found to efficiently eradicate the growth of osteosarcoma, prostate, and

brain tumors both in vitro and in vivo. We observed that androgen-independent human prostate cancer cells lines expressed OC-TK at higher levels than **androgen-dependent** human prostate cancer cell lines. We have obtained data to suggest that Ad-OC-TK plus a pro-drug acyclovir (ACV) may be used as an effective therapy to treat prostate cancer bone metastasis in models where the growth of androgen-independent PC-3 and C4-2 tumors in the bone has occurred.

CT Check Tags: Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Acyclovir: TU, therapeutic use
Androgens: ME, metabolism
Disease Models, Animal
Disease Progression
*Gene Therapy
Osteocalcin: GE, genetics
Osteocalcin: TU, therapeutic use
Prodrugs: TU, therapeutic use
Promoter Regions (Genetics)
Prostate-Specific Antigen: GE, genetics
***Prostatic Neoplasms**
Prostatic Neoplasms: PA, pathology
Prostatic Neoplasms: TH, therapy
Thymidine Kinase: TU, therapeutic use
Tumor Cells, Cultured

RN 104982-03-8 (Osteocalcin); 59277-89-3 (Acyclovir)

CN 0 (Androgens); 0 (Prodrugs); EC 2.7.1.21 (Thymidine Kinase); EC 3.4.21.77 (Prostate-Specific Antigen)

L20 ANSWER 24 OF 48 CANCERLIT on STN

AN 1998082979 CANCERLIT

DN 98082979 PubMed ID: 9422516

TI Androgen receptor gene and hormonal therapy failure of prostate cancer.

AU Koivisto P; Kolmer M; Visakorpi T; Kallioniemi O P

CS Laboratory of Cancer Genetics, Tampere University Hospital and Institute of Medical Technology, University of Tampere, Finland.

SO AMERICAN JOURNAL OF PATHOLOGY, (1998 Jan) 152 (1) 1-9. Ref: 77
Journal code: 0370502. ISSN: 0002-9440.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LA English

FS MEDLINE; Abridged Index Medicus Journals; Priority Journals

OS MEDLINE 1998082979

EM 199801

ED Entered STN: 19980417
Last Updated on STN: 19980417

AB Androgen receptor (AR) is a nuclear transcription factor that binds male sex steroids and mediates the biological effects of these hormones to the target cells, such as the epithelial cells of the prostate gland, by activating transcription of **androgen-dependent** genes. Withdrawal of androgens or the peripheral blockade of androgen action remain the critical therapeutic options for the treatment of advanced prostate cancer. However, after initial regression, many prostate cancers become hormone refractory and progress further with eventual fatal outcome. Understanding the mechanisms of tumor progression and endocrine therapy failure is an important goal. A large number of different molecular mechanisms may be responsible for development of hormone-refractory recurrent tumors. Many of these involve the AR gene and

its complex downstream signaling pathways. The role of AR mutations and altered transactivational properties of the receptor have received the most attention as causative factors for progression. However, other mechanisms, such as AR gene amplification and overexpression or increased local bioconversion of androgens, may contribute to the development of progression by mechanisms that involve **androgen-dependent** cell growth. Here we review the role of the AR gene and its putative downstream effector pathways during human prostate cancer progression and endocrine therapy failure.

CT Check Tags: Human; Male; Support, Non-U.S. Gov't
*Gene Therapy
*Hormones: TU, therapeutic use
***Prostatic Neoplasms: TH, therapy**
*Receptors, Androgen: GE, genetics
Treatment Failure

CN 0 (Hormones); 0 (Receptors, Androgen)

L20 ANSWER 25 OF 48 CANCERLIT on STN
AN 97434302 CANCERLIT
DN 97434302 PubMed ID: 9288188
TI Target to apoptosis: a hopeful weapon for prostate cancer.
AU Tang D G; Porter A T
CS Department of Radiation Oncology, Wayne State University, Detroit, Michigan 48202, USA.. dtang@cms.cc.wayne.edu
SO PROSTATE, (1997 Sep 1) 32 (4) 284-93. Ref: 115
Journal code: 8101368. ISSN: 0270-4137.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 97434302
EM 199709
ED Entered STN: 19971105
Last Updated on STN: 19971105
AB BACKGROUND: Prostate cancer is the most commonly diagnosed neoplasm and the second leading cause of male death in this country. Multiple genetic and epigenetic factors have been implicated in the oncogenesis and progression of prostate cancer. However, the molecular mechanisms underlying the disease remain largely unknown. The major difficulty in the clinical management of prostate cancer stems from the reality that reliable and accurate diagnostic/prognostic biomarkers are not available and that effective treatment regimens for hormone-resistant prostate cancers are yet to be developed. METHODS: The present review, through extensive literature research, summarizes the most recently accumulated experimental and clinical data on the relationship between apoptosis and prostate cancer. We analyze the possibility of inducing prostate cancer cell apoptosis by: 1) androgen ablation by castration or biochemical antagonists: 2) chemotherapeutic drugs or natural/synthetic chemicals; 3) manipulation of apoptosis-related oncoproteins; and 4) modulation of intracellular signal transducers. RESULTS: 1) Prostate cancer, like most other solid tumors, represents a very heterogeneous entity. Most prostate cancers, at the time of clinical diagnosis, present themselves as mixtures of **androgen-dependent** and androgen-independent cells.
2) Most prostate cancers respond initially to androgen ablation since the population of **androgen-dependent** cells undergoes rapid apoptosis upon androgen withdrawal. However, androgen ablation rarely cures patients, most of whom will experience recurrence due to takeover of

the tumor mass by androgen-independent tumor cells as well as the emergence of apoptosis-resistant clones as a result of further genetic alterations such as bcl-2 amplification. 3) On the other hand, although androgen-independent prostate cancer cells do not undergo apoptosis upon androgen blocking, they do maintain the appropriate molecular machinery of apoptosis. Therefore, certain conventional chemotherapy drugs can eliminate androgen-independent cancer cells by inducing apoptosis. 4) However, most drugs used in chemotherapy induce apoptosis or mediate cytotoxicity only in proliferating cancer cells. Human prostate cancer cells demonstrate very slow growth kinetics. Thus, novel chemical/natural products need be identified to eradicate those nonproliferating cancer cells. In this regard, the angiogenesis inhibitor, linomide, and a plant extract, beta-lapachone, demonstrate very promising apoptosis-inducing effects on prostate cancer cells in a proliferation-independent manner. 5) An alternative way to modulate the apoptotic response is by interfering with the expression levels of essential regulatory molecule of apoptosis. Bcl-2 and p53 represent two prime targets for such manipulations. 6) Finally, modulation of signal transduction pathways (e.g., intracellular Ca2+ levels, PKC activity) involved in apoptosis may also induce and/or enhance the apoptotic response of prostate cancer cells. CONCLUSIONS: Modulation of apoptotic response represents a novel mechanism-based approach which may help identify novel drugs and/or develop new therapeutic regimens for the treatment of prostate cancers.

CT Check Tags: Animal; Human; Male
Androgens: PH, physiology
Antineoplastic Agents: TU, therapeutic use
*Apoptosis
Cell Division
Cell Survival
Prostatic Neoplasms: DT, drug therapy
***Prostatic Neoplasms: PA, pathology**
***Prostatic Neoplasms: TH, therapy**
Proto-Oncogene Proteins c-bcl-2: BI, biosynthesis

CN 0 (Androgens); 0 (Antineoplastic Agents); 0 (Proto-Oncogene Proteins c-bcl-2)

L20 ANSWER 26 OF 48 CANCERLIT on STN
AN 97318355 CANCERLIT
DN 97318355 PubMed ID: 9175283
TI Maximal androgen blockade versus total androgen suppression.
AU Dumez H; Van Poppel H; Baert L; Paridaens R
CS Dept. of Oncology and Urology, University Hospitals KULeuven.
SO ACTA UROLOGICA BELGICA, (1997 Mar) 65 (1) 49-54.
Journal code: 0377045. ISSN: 0001-7183.
CY Belgium
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 97318355
EM 199708
ED Entered STN: 19970909
Last Updated on STN: 19970909
AB As long as advanced prostate cancer remains **androgen-dependent**, it can be treated by castration in combination with anti-androgens. When despite maximal androgen blockade (MAB), progression occurs, the anti-androgen withdrawal can result in partial remission. Otherwise corticosteroids can be used in low doses in order to suppress the androgens originating from the adrenal gland: total androgen suppression (TAS). The minimal side effects and the low cost price of this

treatment are important advantages, given the fact that only few efficient cytostatic agents are actually available for hormone-escaped prostate cancer. About 30% of the patients with advanced prostate cancer that became androgen independent will show a secondary remission under low doses hydrocortisone or prednisone.

CT Check Tags: Case Report; Human; Male
Adenocarcinoma: DT, drug therapy
Adenocarcinoma: ME, metabolism
*Adenocarcinoma: TH, therapy
*Androgen Antagonists: TU, therapeutic use
Androgens: BI, biosynthesis
Combined Modality Therapy
Middle Age
Orchiectomy
Prostate-Specific Antigen: BL, blood
Prostatic Neoplasms: DT, drug therapy
Prostatic Neoplasms: ME, metabolism
***Prostatic Neoplasms: TH, therapy**

CN 0 (Androgen Antagonists); 0 (Androgens); EC 3.4.21.77 (Prostate-Specific Antigen)

L20 ANSWER 27 OF 48 CANCERLIT on STN
AN 97153285 CANCERLIT
DN 97153285 PubMed ID: 9000575
TI Androgen receptor gene amplification: a possible molecular mechanism for androgen deprivation therapy failure in prostate cancer.
AU Koivisto P; Kononen J; Palmberg C; Tammela T; Hyytinen E; Isola J; Trapman J; Cleutjens K; Noordzij A; Visakorpi T; Kallioniemi O P
CS Laboratory of Cancer Genetics, Institute of Medical Technology, University of Tampere, Finland.
SO CANCER RESEARCH, (1997 Jan 15) 57 (2) 314-9.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 97153285
EM 199702
ED Entered STN: 19970305
Last Updated on STN: 19970305
AB Progression of prostate cancer during endocrine therapy is a major clinical problem, the molecular mechanisms of which remain poorly understood. Amplification of the androgen receptor (AR) gene was recently described in recurrent prostate carcinomas from patients who had failed androgen deprivation therapy. To evaluate the hypothesis that amplification of the AR gene is a cause for the failure of androgen deprivation therapy in prostate cancer, we studied whether AR amplification leads to gene overexpression, whether the amplified AR gene is structurally intact, and whether tumors with AR amplification have distinct biological and clinical characteristics. Tumor specimens were collected from 54 prostate cancer patients at the time of a local recurrence following therapy failure. In 26 cases, paired primary tumor specimens from the same patients prior to therapy were also available. Fifteen (28%) of the recurrent therapy-resistant tumors, but none of the untreated primary tumors, contained AR gene amplification as determined by fluorescence in situ hybridization. According to single-stranded conformation polymorphism analysis, the AR gene was wild type in all but one of the 13 AR amplified cases studied. In one tumor, a presumed mutation in the hormone-binding domain at codon 674 leading to a Gly -->

Ala substitution was found, but functional studies indicated that this mutation did not change the transactivational properties of the receptor. AR amplification was associated with a substantially increased level of mRNA expression of the gene by in situ hybridization. Clinicopathological correlations indicated that AR amplification was most likely to occur in tumors that had initially responded well to endocrine therapy and whose response duration was more than 12 months. Tumors that recurred earlier or those that showed no initial therapy response did not contain AR amplification. The median survival time after recurrence was two times longer for patients with AR amplification in comparison to those with no amplification (P = 0.03, Willcoxon-Breslow test). In conclusion, failure of conventional androgen deprivation therapy in prostate cancer may be caused by a clonal expansion of tumor cells that are able to continue **androgen-dependent** growth despite of the low concentrations of serum androgens. Amplification and the increased expression of a wild-type AR gene may play a key role in this process.

CT Check Tags: Human; Male; Support, Non-U.S. Gov't
Aged
*Gene Amplification: GE, genetics
In Situ Hybridization, Fluorescence
Middle Age
Neoplasm Recurrence, Local: GE, genetics
Point Mutation
***Prostatic Neoplasms: GE, genetics**
***Prostatic Neoplasms: TH, therapy**
RNA, Messenger: ME, metabolism
*Receptors, Androgen: GE, genetics
Survival Analysis
Treatment Failure

CN 0 (RNA, Messenger); 0 (Receptors, Androgen)

L20 ANSWER 28 OF 48 CANCERLIT on STN
AN 96416207 CANCERLIT
DN 96416207 PubMed ID: 8819113
TI Does an inability to eradicate normal stem cells preclude the cure of some cancers?.
AU Anderson K M; Bonomi P; Harris J E
CS Department of Medicine, Rush Medical College, Chicago, IL 60612, USA.
SO MEDICAL HYPOTHESES, (1996 Jul) 47 (1) 31-4. Ref: 24
Journal code: 7505668. ISSN: 0306-9877.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 96416207
EM 199702
ED Entered STN: 19970305
Last Updated on STN: 19970509
AB Presently, identified signal transduction pathways do not alter normal stem-cell survival. With prostate cancer as a model, the argument is advanced that an inability to eradicate normal **androgen-dependent** prostate stem-cells precludes successful treatment of transformed, androgen-independent and metastatic progeny. While applying this idea to cancers of non-essential organs or to endocrine cancers seems feasible, the inutility of this approach for most other malignancies appears likely, although not certain.
CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't

Apoptosis
Biological Markers
Cell Differentiation
*Cell Transformation, Neoplastic
Evolution
Genes, Homeobox
Models, Biological
Prostaglandins: PH, physiology
*Prostate: PA, pathology
***Prostatic Neoplasms: PA, pathology**
***Prostatic Neoplasms: TH, therapy**
Signal Transduction
*Stem Cells: CY, cytology
Stem Cells: PA, pathology
Stem Cells: RE, radiation effects
Telomerase: ME, metabolism
CN 0 (Biological Markers); 0 (Prostaglandins); EC 2.7.7.- (Telomerase)

L20 ANSWER 29 OF 48 CANCERLIT on STN
AN 96369502 CANCERLIT
DN 96369502 PubMed ID: 8773508
TI How is **androgen-dependent** metastatic prostate cancer best treated?.
AU Robson M; Dawson N
CS Uniformed Services University of the Health Sciences, Bethesda, Maryland, USA.
SO HEMATOLOGY/ONCOLOGY CLINICS OF NORTH AMERICA, (1996 Jun) 10 (3) 727-47. Ref: 149
Journal code: 8709473. ISSN: 0889-8588.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 96369502
EM 199612
ED Entered STN: 19970108
Last Updated on STN: 19970108
AB The principles of management of newly diagnosed metastatic prostate cancer have changed little since the time of Huggins and his colleagues. Modern clinicians have many more weapons in their therapeutic armamentarium than those pioneers, but little progress has been made in improving the survival of men with this disease. The results of androgen deprivation are comparable using any one of a number of different monotherapy approaches. The use of combined androgen blockade may improve survival in men with minimal disease but at considerable economic cost and with significant impairment of quality of life. The benefit of this therapy for men with more extensive disease is uncertain. New modalities such as intermittent androgen blockade or combination therapies are exciting, but unproven.
CT Check Tags: Comparative Study; Human; Male
Adenocarcinoma: PP, physiopathology
Adenocarcinoma: SC, secondary
*Adenocarcinoma: TH, therapy
Androgen Antagonists: TU, therapeutic use
*Androgens: PH, physiology
Combined Modality Therapy
Orchiectomy
Prognosis

Prostatic Neoplasms: PA, pathology
Prostatic Neoplasms: PP, physiopathology
***Prostatic Neoplasms: TH, therapy**
Treatment Outcome
CN 0 (Androgen Antagonists); 0 (Androgens)

L20 ANSWER 30 OF 48 CANCERLIT on STN
AN 96119515 CANCERLIT
DN 96119515 PubMed ID: 8561879
TI Active immunization against LHRH alone or combined with LHRH-analogue treatment impedes growth of **androgen-dependent** prostatic carcinoma.
AU Ladd A; Walfield A; Tsong Y Y; Thau R
CS Population Council, Center for Biomedical Research, New York, New York, USA.
NC HD 13541 (NICHD)
SO AMERICAN JOURNAL OF REPRODUCTIVE IMMUNOLOGY, (1995 Sep) 34 (3) 200-6. Journal code: 8912860. ISSN: 1046-7408.
CY Denmark
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 96119515
EM 199603
ED Entered STN: 19960424
Last Updated on STN: 19960424
AB PROBLEM: To determine whether active immunization against LHRH can serve as treatment for **androgen-dependent** prostatic carcinoma. METHOD: Male rats of Copenhagen X Fisher strain, implanted with Dunning R-3327 prostatic carcinoma cells were either immunized against LHRH, treated with LHRH-antagonist, or received a combined treatment of active immunization against LHRH and LHRH-antagonist. RESULTS: Testicular histology was consistent with infertility in all treatment groups. The rate of tumor growth was inhibited by all three treatment regimens. Tumor size increased by 3.8 +/- 1.4 cm2 in the LHRH-antagonist group, 3.2 +/- 1.1 cm2 in the immunized group, and 1.0 +/- 0.4 cm2 in the combined treatment group, as compared to 8.2 +/- 2.6 cm2 in non-treated control group. CONCLUSION: LHRH-antagonist administration combined with immunization against LHRH appeared to exert a synergistic effect. This may be due to the blockade of prostatic LHRH-like receptors by the antagonist, while androgen depletion was rapidly achieved by LHRH-antagonist, and maintained by continued gonadotropin suppression caused by active immunization against LHRH once antagonist treatment had been discontinued.
CT Check Tags: Animal; Male; Support, U.S. Gov't, P.H.S.
Androgen Antagonists: TU, therapeutic use
*Androgens: PH, physiology
Antibodies: BL, blood
Carcinoma: IM, immunology
Carcinoma: PA, pathology
*Carcinoma: TH, therapy
Cell Division: DE, drug effects
Drug Therapy, Combination
Gonadorelin: AA, analogs & derivatives
*Gonadorelin: IM, immunology
Gonadorelin: TU, therapeutic use
Immunity, Active
*Immunotherapy
Immunotherapy: MT, methods
Immunotoxins: TU, therapeutic use

Organ Weight: DE, drug effects
Prostatic Neoplasms: IM, immunology
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**
Rats
Testis: DE, drug effects
Testosterone: BL, blood
Tetanus Toxoid: TU, therapeutic use
RN 33515-09-2 (Gonadorelin); 57-85-2 (Testosterone)
CN 0 (Androgen Antagonists); 0 (Androgens); 0 (Antibodies); 0 (Immunotoxins); 0 (Tetanus Toxoid)

L20 ANSWER 31 OF 48 CANCERLIT on STN
AN 96004111 CANCERLIT
DN 96004111 PubMed ID: 7483155
TI [Theoretical considerations and initial clinical results of intermittent hormone treatment of patients with advanced prostatic carcinoma]. Theoretische Uberlegungen und erste klinische Ergebnisse mit intermittierender Hormonbehandlung bei Patienten mit einem fortgeschrittenen Prostatakarzinom.
AU Bruchovsky N; Goldenberg S L; Rennie P S; Gleave M
CS Department of Cancer Endocrinology, Vancouver, Canada.
SO UROLOGE. AUSGABE A, (1995 Sep) 34 (5) 389-92. Ref: 8
Journal code: 1304110. ISSN: 0340-2592.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA German
FS MEDLINE; Priority Journals
OS MEDLINE 96004111
EM 199512
ED Entered STN: 19960126
Last Updated on STN: 19960126
AB Androgen suppression is the routine approach to the treatment of advanced prostate cancer. Using intermittent androgen suppression by taking the advantage of the reversible action of medical castration results in the maintenance of apoptotic potential. The experiments in the **androgen-dependent androgen-dependent** Shionogi carcinoma tumor model as well as clinical experience in a group of men with prostate malignancy are presented in this report. These consecutive cycles of androgen withdrawal and replacement afford an improved quality of life when the patient is off therapy. It is possible to reduce toxicity, cost of treatment and to delay tumor progression. Whether survival is affected in a beneficial or adverse way still remains to be studied.
CT Check Tags: Animal; Human; Male
Androgen Antagonists: AD, administration & dosage
Androgen Antagonists: AE, adverse effects
Antineoplastic Agents, Hormonal: AD, administration & dosage
*Antineoplastic Agents, Hormonal: AE, adverse effects
Combined Modality Therapy
English Abstract
Neoplasm Staging
Neoplasms, Hormone-Dependent: MO, mortality
Neoplasms, Hormone-Dependent: PA, pathology
*Neoplasms, Hormone-Dependent: TH, therapy
Orchiectomy
Prostatic Neoplasms: MO, mortality

Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**
Survival Rate
CN 0 (Androgen Antagonists); 0 (Antineoplastic Agents, Hormonal)

L20 ANSWER 32 OF 48 CANCERLIT on STN
AN 95297586 CANCERLIT
DN 95297586 PubMed ID: 7778676
TI Castration therapy rapidly induces apoptosis in a minority and decreases cell proliferation in a majority of human prostatic tumors.
AU Westin P; Stattin P; Damber J E; Bergh A
CS Department of Pathology, University of Umea, Sweden.
SO AMERICAN JOURNAL OF PATHOLOGY, (1995 Jun) 146 (6) 1368-75.
Journal code: 0370502. ISSN: 0002-9440.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Abridged Index Medicus Journals; Priority Journals
OS MEDLINE 95297586
EM 199507
ED Entered STN: 19950809
Last Updated on STN: 19970509
AB Major differences in the long-term clinical response to castration therapy of prostatic carcinoma suggests intertumoral differences in cellular response and defines a need for identification of patients with an eventually positive outcome as well as those in need of additional treatment. Using morphometry, monoclonal antibodies against Bcl-2, c-myc, Ki-67, and p53 proteins, and an in situ method to visualize apoptotic cells, we examined the short-term response of prostatic tumors to castration in core biopsies from 18 prostatic cancer patients taken the day before and 7 days after castration. At the histological level, 3 tumors seemed practically unaffected by castration. In 15 tumors, castration induced vacuolization of tumor cell cytoplasm and decreases in nuclear area and Ki-67 index. In these 15 tumors, apoptotic index was significantly increased in 6, principally unaffected in 6, and decreased in 3. The 6 tumors responding with an increase in apoptotic index were WHO grade 1 or 2 and negative for p53, c-myc, and Bcl-2 or contained only few Bcl-2- or c-myc-positive tumor cells before therapy. The 12 tumors in which apoptotic index was unaffected or decreased were WHO grade 2 or 3 and immunopositive for one or more of p53, Bcl-2, and c-myc proteins before therapy. The Bcl-2 index was significantly increased in 10 patients. Prostatic tumors may respond in a variety of possibly predictable ways to castration therapy including a decrease in apoptotic index. The magnitude of these responses are not correlated in individual tumors, suggesting that the common classification of prostatic tumors as either **androgen dependent** (dying after castration) or independent (not responding at all to castration) may be an oversimplification.
CT Check Tags: Human; Male; Support, Non-U.S. Gov't
*Apoptosis: PH, physiology
*Castration: UT, utilization
*Cell Division: PH, physiology
Genetic Techniques
Image Processing, Computer-Assisted
Immunoenzyme Techniques
Ki-67 Antigen
Neoplasm Proteins: IM, immunology
Nuclear Proteins: IM, immunology
***Prostatic Neoplasms: PA, pathology**

***Prostatic Neoplasms: TH, therapy**
Protein p53: AN, analysis
Proto-Oncogene Proteins: AN, analysis
Proto-Oncogene Proteins c-bcl-2
Proto-Oncogene Proteins c-myc: AN, analysis
CN 0 (Ki-67 Antigen); 0 (Neoplasm Proteins); 0 (Nuclear Proteins); 0 (Protein p53); 0 (Proto-Oncogene Proteins); 0 (Proto-Oncogene Proteins c-bcl-2); 0 (Proto-Oncogene Proteins c-myc)

L20 ANSWER 33 OF 48 CANCERLIT on STN
AN 95252897 CANCERLIT
DN 95252897 PubMed ID: 7735002
TI Androgen action: molecular mechanism and medical application.
AU Liao S
CS Ben May Institute, Department of Biochemistry and Molecular Biology, University of Chicago, Illinois 60637, USA.
NC CA 59073 (NCI)
DK 37694 (NIDDK)
DK41670 (NIDDK)
SO JOURNAL OF THE FORMOSAN MEDICAL ASSOCIATION, (1994 Sep) 93 (9) 741-51. Ref: 85
Journal code: 9214933. ISSN: 0929-6646.
CY TAIWAN: Taiwan, Province of China
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 95252897
EM 199506
ED Entered STN: 19950707
Last Updated on STN: 19950707
AB Androgen action in many organs, such as prostate and skin, is dependent on the conversion of testosterone by 5 alpha-reductase to 5 alpha-dihydrotestosterone. 5 alpha-Dihydrotestosterone then binds to the androgen receptor to regulate specific gene expression. Inhibitors of 5 alpha-reductase are useful for the selective treatment of prostatic cancer, benign prostate hyperplasia, acne, baldness and female hirsutism, without affecting spermatogenesis, sexual behavior and smooth muscle growth, that do not require the conversion of testosterone to 5 alpha-dihydrotestosterone. Certain unsaturated fatty acids, such as gamma-linolenic acid, are potent 5 alpha-reductase inhibitors, suggesting a linkage between unsaturated fatty acids and androgen action. Mutations in androgen receptor genes are responsible for many cases of androgen-insensitivity. In some prostate cancer cells, some antiandrogens may act like androgens in stimulating the proliferation of the cancer cells because these antiandrogens can bind to a mutated androgen receptor and transactivate target genes. Prostate cancers are usually **androgen-dependent** initially but can lose dependency and responsiveness. Tumor cells which are resistant to endocrine therapy ultimately proliferate. Androgen-independent or androgen-repressive cells can arise from androgen-sensitive prostate cancer cells by changes in specific gene expression over time in a clonal isolate. This change in androgen responsiveness was accompanied by a change in androgen receptor expression and transcriptional activity as well as expression of some oncogenes.
CT Check Tags: Human; Male; Support, U.S. Gov't, P.H.S.
Androgen Antagonists: ME, metabolism
Androgens: CH, chemistry

Androgens: GE, genetics
Androgens: ME, metabolism
*Androgens: PH, physiology
Base Sequence
Molecular Sequence Data
Prostatic Neoplasms: GE, genetics
Prostatic Neoplasms: ME, metabolism
Prostatic Neoplasms: TH, therapy
Receptors, Androgen: CH, chemistry
Receptors, Androgen: GE, genetics
Receptors, Androgen: PH, physiology
Skin Diseases: GE, genetics
Skin Diseases: ME, metabolism
Testosterone 5-alpha-Reductase: AI, antagonists & inhibitors
Testosterone 5-alpha-Reductase: GE, genetics
Testosterone 5-alpha-Reductase: ME, metabolism
Testosterone 5-alpha-Reductase: PH, physiology
CN 0 (Androgen Antagonists); 0 (Androgens); 0 (Receptors, Androgen); EC 1.3.99.5 (Testosterone 5-alpha-Reductase)

L20 ANSWER 34 OF 48 CANCERLIT on STN
AN 95187206 CANCERLIT
DN 95187206 PubMed ID: 7881465
TI Apoptosis: therapeutic significance in the treatment of **androgen -dependent** and androgen-independent prostate cancer.
AU Kyprianou N
CS Department of Surgery, University of Maryland Medical Center, Baltimore 21201.
SO WORLD JOURNAL OF UROLOGY, (1994) 12 (6) 299-303. Ref: 48
Journal code: 8307716. ISSN: 0724-4983.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 95187206
EM 199504
ED Entered STN: 19950509
Last Updated on STN: 19970509
AB To improve survival in men with metastatic prostatic cancer, a therapeutic modality that can effectively eliminate androgen-independent cancer cells is needed desperately. Combination of such an effective modality with androgen ablation could affect all of the heterogeneous populations within prostate tumors of individual patients, thus optimizing the chances of complete cure. Such a therapeutic approach will probably require two types of agents, one with antiproliferative activity affecting the small number of dividing androgen-independent cells and one with the capacity to increase the rate of cell death among the non-proliferating androgen-independent prostatic cancer cells present, i.e. the majority. Androgen-responsive human prostate cancer cells are able to undergo programmed cell death after androgen ablation (even if the cells are not in the proliferative cell cycle). Androgen-independent human prostate cancer cells, however, do not activate this apoptotic pathway of cell death in response to androgen ablation. In contrast, androgen-independent human prostate cancer cells can be induced to undergo apoptosis following such alternative treatment modalities as: (a) non-androgen ablative cytotoxic drugs, such as fluorinated pyrimidines, which result in the "thymine-less state", and (b) ionizing irradiation. The apoptotic effect

induced by radiation can be significantly potentiated by post-irradiation treatment of the cells with suramin. In contrast, this radiation induced apoptosis can be substantially inhibited by pretreatment of cells with suramin, probably through suramin's ability to arrest proliferating cells in the GO/G1 phase of the cell cycle. These results suggest that treatment of prostate cancer patients with suramin prior to irradiation is likely to inhibit radiation palliation.(ABSTRACT TRUNCATED AT 250 WORDS)

CT Check Tags: Animal; Human; Male
*Androgens: PH, physiology
Antineoplastic Agents: TU, therapeutic use
*Apoptosis
Combined Modality Therapy
Prostate: PA, pathology
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**
*Suramin: TU, therapeutic use
Tumor Cells, Cultured

RN 145-63-1 (Suramin)

CN 0 (Androgens); 0 (Antineoplastic Agents)

L20 ANSWER 35 OF 48 CANCERLIT on STN

AN 94365156 CANCERLIT

DN 94365156 PubMed ID: 8083332

TI Experimental study of the effects of hormonal therapy and intralesional injections of interleukin 2, activated macrophages on mouse prostate cancer models.

AU Ikeda K

CS Department of Urology, Nippon Medical School, Tokyo, Japan.

SO NIPPON IKA DAIGAKU ZASSHI. JOURNAL OF THE NIPPON MEDICAL SCHOOL, (1994 Aug) 61 (4) 278-85.
Journal code: 7505726. ISSN: 0048-0444.

CY Japan

DT Journal; Article; (JOURNAL ARTICLE)

LA Japanese

FS MEDLINE; Priority Journals

OS MEDLINE 94365156

EM 199410

ED Entered STN: 19941116
Last Updated on STN: 19941116

AB In order to establish a more effective and safer therapy for **androgen-dependent** prostate cancer, to be used in addition to hormonal therapy, the anti-tumor effects of intralesionally administered macrophages activated with recombinant interferon-gamma (INF-gamma), alone or in combination with recombinant interleukin-2 (IL-2) were studied in mouse prostate cancer models. Firstly, in terms of cellular adoptive immunotherapy, phagocytosis against Latex bead and cytotoxicity against Shionogi 115 cancer cell line (SC115) of macrophages activated with INF-gamma for 24 hour were investigated. One ml of 0.25% glycogen solution was intraperitoneally administered to male DS mice. Three days later, fluid was aspirated from the abdominal cavity and macrophages were separated for use in this experiment. Phagocytosis INF-gamma-dose-dependently increased and macrophages activated with 100 U/ml INF-gamma phagocytosed 78.3 +/- 4.5% (mean +/- SD) Latex bead. Cytotoxicity (modified MTT assay) of SC 115 by macrophages activated with 100 U/ml INF-gamma increased remarkably in comparison with non-activated macrophages and there was a significant increase in the effector-to-target-cell ratio to 40 in the activated group 77 +/- 4.3% (mean +/- SD) relative to 50 +/- 6.3% (mean +/- SD) in the non-activated group. Based on these in vitro findings, hormonal therapy and adoptive

local immunotherapy, alone or together, were studied in mouse prostate cancer models. The prostate cancer model was prepared through the subcutaneous transplantation of SC115 in male DS mice and the treatments were initiated after tumors were palpable. The therapy protocols were as follows: Group I control and Group II received 20 mg/kg/day diethylstilbestrol diphosphate (DES-P) subcutaneously for 10 days, Group III received DES-P in combination with ten thousand units of IL-2 administered five times intralesionally, Group IV received DES-P in combination with 2 x 10(6) macrophages activated with 100 U/ml INF-gamma administered three times intralesionally, Group V received DES-P and IL-2 in combination with activated macrophages. The therapeutic efficiencies were evaluated by calculating the tumor volume and survival time. The results of the tumor volume on the 40th day post tumor transplantation were as follows (mean +/- SD): Group I 7,049 +/- 1,477 mm3, Group II 4,495 +/- 654 mm3, Group III 2,050 +/- 724 mm3, Group IV 2,782 +/- 970 mm3, Group V 1,555 +/- 514 mm3. The therapeutic groups showed significant tumor reduction relative to the control. Furthermore, intralesionally IL-2, the activated macrophages injected groups, alone or together, were more effective relative to the group receiving only DES-P.(ABSTRACT TRUNCATED AT 400 WORDS)

CT Check Tags: Animal; Male
*Antineoplastic Agents: TU, therapeutic use
*Diethylstilbestrol: AA, analogs & derivatives
Diethylstilbestrol: TU, therapeutic use
English Abstract
Immunotherapy: MT, methods
Injections, Intralesional
Interferon Type II: PD, pharmacology
*Interleukin-2: AD, administration & dosage
Macrophage Activation
*Macrophages: IM, immunology
Mice
***Prostatic Neoplasms: TH, therapy**
Recombinant Proteins: AD, administration & dosage

RN 13425-53-1 (fosfestrol); 56-53-1 (Diethylstilbestrol); 82115-62-6 (Interferon Type II)

CN 0 (Antineoplastic Agents); 0 (Interleukin-2); 0 (Recombinant Proteins)

L20 ANSWER 36 OF 48 CANCERLIT on STN
AN 93153721 CANCERLIT
DN 93153721 PubMed ID: 7679038
TI Basis for hormonal management of advanced prostate cancer.
AU Geller J
CS Department of Medical Education, Mercy Hospital and Medical Center, San Diego, CA 92103-2180.
SO CANCER, (1993 Feb 1) 71 (3 Suppl) 1039-45.
Journal code: 0374236. ISSN: 0008-543X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Abridged Index Medicus Journals; Priority Journals
OS MEDLINE 93153721
EM 199303
ED Entered STN: 19941107
Last Updated on STN: 19960517
AB BACKGROUND. In the early 1940s, when it was established that most prostatic cancers were **androgen dependent** and could be controlled by androgen withdrawal, little was known about the mechanism of androgen action. Measurements of hormones, both in the circulation and in

the tissue, were not available, nor were measurements of androgen receptors known at that time. METHODS. Since that time, a large body of information has been published regarding the mechanism of androgen-mediated action. With the understanding of androgen-mediated action has come the opportunity to develop drugs targeted to block specific steps in the sequence of androgen action, beginning in the hypothalamus-pituitary area and extending down to the intracellular processes of enzymatic reduction, receptor binding, and nuclear translocation of the hormone receptor complexes. The major focus in prostate cancer therapy currently is the role of the adrenal androgens. RESULTS. It was established in the 1970s that, after castration, there was a 75% reduction in the dihydrotestosterone (DHT) present in prostate tissue. This observation contrasted with the finding that there was a greater than 90% reduction in circulating testosterone levels in the plasma after castration. Based on this important observation regarding tissue DHT concentrations after castration, attempts were made in the 1980s to block androgen totally using simultaneous gonadal and adrenal suppression. Dramatic results were reported after this type of therapy in the early uncontrolled studies. A luteinizing hormone-releasing hormone agonist plus flutamide was used for total androgen blockade. Other techniques for such blockade were available using megestrol acetate in combination with 17-beta-estradiol. One of the key issues has been whether the 25% residual DHT after castration provides a sufficient stimulus to growth of residual prostate tumor cells. The best evidence for the importance of the role of adrenal androgens came from clinical studies in which objective clinical responses were found in patients treated with various inhibitors of androgen action after relapse and castration. If "objectively stable" is included as a category after treatment, then approximately 33% of patients who have relapses after castration can be shown to have an additional response, albeit short, to adrenal androgen withdrawal. CONCLUSIONS. Thus, the control of the relatively small amounts of DHT remaining after castration became a major focus for therapy in metastatic prostate cancer.

CT Check Tags: Animal; Human; Male
Androstenedione: ME, metabolism
Neoplasm Recurrence, Local: DT, drug therapy
*Neoplasms, Hormone-Dependent: ME, metabolism
Neoplasms, Hormone-Dependent: TH, therapy
*Orchiectomy
Prasterone: ME, metabolism
Prostate: GD, growth & development
*Prostate: ME, metabolism
Prostate-Specific Antigen: ME, metabolism
Prostatic Hyperplasia: ME, metabolism
***Prostatic Neoplasms: ME, metabolism**
Prostatic Neoplasms: TH, therapy
Proteins: BI, biosynthesis
Rats
Stanolone: AI, antagonists & inhibitors
*Stanolone: ME, metabolism
Testosterone: AD, administration & dosage
*Testosterone: ME, metabolism

RN 521-18-6 (Stanolone); 53-43-0 (Prasterone); 57-85-2 (Testosterone); 63-05-8 (Androstenedione)

CN 0 (Proteins); EC 3.4.21.77 (Prostate-Specific Antigen)

L20 ANSWER 37 OF 48 CANCERLIT on STN

AN 93046217 CANCERLIT

DN 93046217 PubMed ID: 1841755

TI Programmed cell death as a new target for prostatic cancer therapy.
AU Kyprianou N; Martikainen P; Davis L; English H F; Isaacs J T
CS Johns Hopkins Oncology Center, Baltimore, Maryland 21205.
SO CANCER SURVEYS, (1991) 11 265-77. Ref: 68
Journal code: 8218015. ISSN: 0261-2429.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 93046217
EM 199212
ED Entered STN: 19941107
Last Updated on STN: 19941107
AB To increase survival of men with metastatic prostatic cancer, a modality that can effectively eliminate androgen independent cancer cells is desperately needed. By combining such an effective modality with androgen ablation, all of the heterogeneous populations of tumour cells within a prostatic cancer patient can be affected, thus optimizing the chances of cure. Unfortunately, such effective therapy for the androgen independent prostatic cancer cell is not yet available. This therapy will probably require two types of agents, one having antiproliferative activity affecting the small number of dividing androgen independent cells, and the other able to increase the low rate of cell death among the majority of non-proliferating (ie interphase) androgen independent prostatic cancer cells present. **Androgen dependent** prostatic epithelial cells can be made to undergo programmed death by means of androgen ablation, even if the cells are not in the proliferative cell cycle. Androgen independent prostatic cancer cells retain the major portion of this programmed cell death pathway, only there is a defect in the pathway such that it is no longer activated by androgen ablation. If the intracellular free Ca2+ is sustained at an elevated level for a sufficient time, androgen independent cells can be induced to undergo programmed death. The long term goal is therefore to develop some type of non-androgen ablative method that can be used in vivo to induce a sustained elevation in Ca2+ in androgen independent prostatic cancer cells. To accomplish this task, a more complete understanding of the biochemical pathways involved in programmed cell death is urgently needed. At present, studies are focusing on the mechanism involved in the Ca2+ elevation in the normal and malignant **androgen dependent** cell induced following androgen ablation and the role of the TRPM-2 protein in this process.
CT Check Tags: Animal; Human; Male
Adenocarcinoma: SU, surgery
*Adenocarcinoma: TH, therapy
Androgens: PH, physiology
Calcium: PH, physiology
Castration
Cell Death: PH, physiology
Prostatic Neoplasms: SU, surgery
***Prostatic Neoplasms: TH, therapy**
Rats
RN 7440-70-2 (Calcium)
CN 0 (Androgens)

L20 ANSWER 38 OF 48 CANCERLIT on STN
AN 92056295 CANCERLIT
DN 92056295 PubMed ID: 1949430

TI GM-CSF restoration of a differentiated (growth factor-regulated) phenotype in an anaplastic tumor.
AU Rubenstein M; Shaw M; Targonski P; McKiel C F; Dubin A; Guinan P
CS Department of Research Biochemistry, Hektoen Institute for Medical Research, Chicago.
SO UROLOGICAL RESEARCH, (1991) 19 (5) 309-12.
Journal code: 0364311. ISSN: 0300-5623.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 92056295
EM 199112
ED Entered STN: 19941107
Last Updated on STN: 19941107
AB GM-CSF (granulocyte-macrophage-derived colony-stimulating factor) is a differentiation agent that stimulates bone marrow activity in patients receiving chemotherapy. GM-CSF (1 microgram/ml daily for 10 days), administered intralesionally, was evaluated to determine whether it would restore a more differentiated phenotype to an anaplastic, rapidly growing, hormone-independent variant (R3327 MAT-LyLu) of the Dunning prostatic adenocarcinoma. Immunohistology was used to quantitate the expression of epithelial growth factor receptors (rEGF) and the tissue testosterone content. GM-CSF therapy significantly (P less than 0.05) restored rEGF expression and tissue testosterone to levels associated with better differentiated, slower growing, **androgen-dependent** Dunning variants (R3327 H and G). GM-CSF may have a role in treatment of prostatic cancers by promoting androgen and epithelial growth factor regulation.
CT Check Tags: Animal; Comparative Study; Male
Adenocarcinoma: CH, chemistry
Adenocarcinoma: GE, genetics
*Adenocarcinoma: TH, therapy
*Granulocyte-Macrophage Colony-Stimulating Factor: TU, therapeutic use
Neoplasm Transplantation
Phenotype
Prostatic Neoplasms: CH, chemistry
Prostatic Neoplasms: GE, genetics
***Prostatic Neoplasms: TH, therapy**
Rats
Rats, Inbred Strains
Receptor, Epidermal Growth Factor: AN, analysis
Recombinant Proteins: TU, therapeutic use
Testosterone: AN, analysis
RN 57-85-2 (Testosterone); 83869-56-1 (Granulocyte-Macrophage Colony-Stimulating Factor)
CN 0 (Recombinant Proteins); EC 2.7.11.- (Receptor, Epidermal Growth Factor)

L20 ANSWER 39 OF 48 CANCERLIT on STN
AN 88268126 CANCERLIT
DN 88268126 PubMed ID: 3389834
TI Prostatic carcinoma. I: Androgen dependency of prostatic carcinoma.
AU Shimazaki J; Fuse H; Akimoto S; Sumiya H; Akakura K; Ichikawa T
CS Dept. of Urology, School of Medicine, Chiba University.
SO GAN TO KAGAKU RYOHO [JAPANESE JOURNAL OF CANCER AND CHEMOTHERAPY], (1988 Apr) 15 (4 Pt 2-1) 909-16.
Journal code: 7810034. ISSN: 0385-0684.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)

LA Japanese
FS MEDLINE; Priority Journals
OS MEDLINE 88268126
EM 198807
ED Entered STN: 19941107
Last Updated on STN: 19941107
AB Endocrine therapy, which consists of orchiectomy followed by administration of large doses of estrogen, then a reduced amount of estrogen, has been applied as the main treatment for stage D2 prostatic cancer. Alternatively, anti-androgen is used for elderly patients or those with cardiovascular disorders. Survival rate with endocrine therapy at 5 and 10 years was 35% and 16%, respectively. Therefore, in Japan, a better survival is shown than that reported in western countries using much smaller doses of estrogen. Most of the side effects caused by estrogen are not serious. Side effects caused by anti-androgen are few except for loss of libido. At the start of treatment, more than 80% of patients showed a response, but gradually relapse occurred and only 20% were well controlled 5 years after the start. Factors influencing the survival were pathological grade, response to endocrine therapy judged by the level of prostatic acid phosphatase 4 weeks after the start, and R1881 (methyltrienolone)-binding protein observed histochemically. The latter protein was also correlated with the grade and response to endocrine therapy. Relapse after endocrine therapy might be attributable to adaptation or mutation progressing to androgen-independent cells. Using SC 115, an **androgen-dependent** mouse tumor, these two types of relapse were demonstrated. Gradual progression to undifferentiated cancer was noticed between pretreatment biopsy and autopsy. Relapse in human prostatic cancer may thus be partly due to genetic change to a resistant clone.
CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't
Androgen Antagonists: TU, therapeutic use
*Androgens: PH, physiology
English Abstract
Estrogens: TU, therapeutic use
Mice
*Neoplasms, Hormone-Dependent: PP, physiopathology
Neoplasms, Hormone-Dependent: TH, therapy
Orchiectomy
***Prostatic Neoplasms: PP, physiopathology**
Prostatic Neoplasms: TH, therapy
CN 0 (Androgen Antagonists); 0 (Androgens); 0 (Estrogens)

L20 ANSWER 40 OF 48 CANCERLIT on STN
AN 88237065 CANCERLIT
DN 88237065 PubMed ID: 2453965
TI [Recent findings on the pathogenesis and therapy of prostatic cancer]. Neuere Aspekte zur Pathogenese und Therapie des Prostatakarzinoms.
AU Schulze H; Isaacs J T; Senge T
CS Urologische Klinik, Ruhr-Universitat Bochum, Marienhospital Herne, Bundesrepublik Deutschland.
SO UROLOGE. AUSGABE A, (1988 Mar) 27 (2) 105-10. Ref: 52
Journal code: 1304110. ISSN: 0340-2592.
CY GERMANY, WEST: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA German
FS MEDLINE; Priority Journals
OS MEDLINE 88237065

EM 198806
ED Entered STN: 19941107
Last Updated on STN: 19960517
AB Presently, there is no effective therapy for increasing survival of metastatic prostatic cancer. New approaches to this major disease are, therefore, urgently needed. One approach is to study the biology of prostatic carcinogenesis in order to develop a therapeutic modality to prevent the development of clinically manifest prostatic cancer. Based upon international epidemiological data, it should be possible to lower the incidence of clinical prostatic cancer by more than 10-fold among the males of the western industrial states. An alternative approach is to study the tumor biology of prostatic cancer in order to identify new modalities to better treat already established clinical prostatic cancer. Such studies have already demonstrated that individual prostatic cancers are composed of clones of cancer cells which are phenotypically heterogeneous even before therapy is initiated. Due to this tumor cell heterogeneity, the direction of future studies should be towards combining androgen ablation plus chemotherapy early in the disease in order to affect both the **androgen-dependent** and -independent cancer cells present within individual prostatic cancers.
CT Check Tags: Animal; Human; Male
*Cell Transformation, Neoplastic: PA, pathology
Combined Modality Therapy
English Abstract
Prostate: PA, pathology
*Prostatic Hyperplasia: PA, pathology
***Prostatic Neoplasms: PA, pathology**
Prostatic Neoplasms: TH, therapy

L20 ANSWER 41 OF 48 CANCERLIT on STN
AN 87320737 CANCERLIT
DN 87320737 PubMed ID: 3307086
TI Development of androgen-independent tumor cells and their implication for the treatment of prostatic cancer.
AU Isaacs J T; Kyprianou N
NC CA 15416 (NCI)
SO UROLOGICAL RESEARCH, (1987) 15 (3) 133-8. Ref: 40
Journal code: 0364311. ISSN: 0300-5623.
CY GERMANY, WEST: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 87320737
EM 198710
ED Entered STN: 19941107
Last Updated on STN: 19941107
AB Development of androgen-independent prostatic cancer cells from androgen-responsive cells can occur by a variety of mechanisms (e.g., environmental adaptation, multifocal origin, or genetic instability). Regardless of the mechanism of development, however, once androgen-independent cancer cells become present within prostatic cancer, the tumor is no longer homogeneous but is now heterogeneous. Once a prostatic cancer is heterogeneously composed of both **androgen-dependent** and -independent cancer cells, androgen withdrawal therapy, no matter how complete, cannot be curative. In order to produce cures of such heterogeneous prostatic cancers, hormonal therapy must be combined simultaneously with chemotherapy early in the course of the disease so that all the cancer populations (i.e., **androgen-**

dependent and -independent) can be simultaneously affected within an individual patient.

CT Check Tags: Human; Male; Support, U.S. Gov't, P.H.S.
Androgen Antagonists: TU, therapeutic use
*Androgens: PH, physiology
Cell Differentiation
Combined Modality Therapy
Cyclophosphamide: PD, pharmacology
Cyclophosphamide: TU, therapeutic use
Flutamide: TU, therapeutic use
Gonadorelin: PD, pharmacology
Gonadorelin: TU, therapeutic use
Orchiectomy
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**

RN 13311-84-7 (Flutamide); 33515-09-2 (Gonadorelin); 50-18-0 (Cyclophosphamide)

CN 0 (Androgen Antagonists); 0 (Androgens)

L20 ANSWER 42 OF 48 CANCERLIT on STN
AN 87311066 CANCERLIT
DN 87311066 PubMed ID: 3625464
TI Effects of olfactory bulbectomy, melatonin, and/or pinealectomy on three sublines of the Dunning R3327 rat prostatic adenocarcinoma.
AU Toma J G; Amerongen H M; Hennes S C; O'Brien M G; McBlain W A; Buzzell G R
SO JOURNAL OF PINEAL RESEARCH, (1987) 4 (3) 321-38.
Journal code: 8504412. ISSN: 0742-3098.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 87311066
EM 198710
ED Entered STN: 19941107
Last Updated on STN: 19970509
AB Conventional antiandrogen therapy for prostatic cancer generally results in the death of **androgen-dependent** cells, resulting in shrinkage of the tumor, followed by regrowth of the tumor as androgen-insensitive cells take over. Because of reported antigonadotropic and antineoplastic effects of the pineal hormone melatonin (MEL), we hypothesized that this indole might provide an effective therapy for prostate cancer, as it would be effective against both populations of tumor cells. We used three sublines of the Dunning R3327 rat prostatic adenocarcinoma to determine whether MEL could suppress the growth of these tumors and, if so, by what mechanisms this occurs. In one experiments, we compared the growth of a well-differentiated slow-growing Dunning tumor in rats given MEL combined with the potentiating procedure olfactory bulbectomy (BULBX), with that in rats pinealectomized (PINX) or untreated. Tumor growth in BULBX-MEL rats was significantly suppressed over that in the other two groups, as were the weights of the gonads and accessory sex glands. Tumor morphology, DNA concentration, and androgen receptor concentration and distribution were identical in untreated controls and in BULBX-MEL rats, suggesting that the treatment affected all populations of tumor cells equally. With another strain of well-differentiated slow-growing Dunning tumor, we examined the effects of MEL in rats with and without BULBX. Reproductive parameters were not suppressed in BULBX-MEL rats and, while there was a trend toward slower tumor growth in this group, this was not significant. Intact rats given MEL grew larger tumors than did control rats but, again, differences were not significant.

In a third experiment, we examined a fast-growing androgen-insensitive anaplastic Dunning tumor. PINX was without effect on this tumor, but BULBX-MEL resulted in a significant suppression of one of the constants in the logistic equation fitted to the growth curves. This indicates that there were some direct antitumor effects of BULBX-MEL on this tumor strain. We conclude that MEL suppresses growth of some Dunning tumor strains.

CT Check Tags: Animal; Male; Support, Non-U.S. Gov't
Adenocarcinoma: ME, metabolism
*Adenocarcinoma: PA, pathology
Adenocarcinoma: TH, therapy
Androgens: PH, physiology
DNA: ME, metabolism
Genitalia, Male: PA, pathology
*Melatonin: TU, therapeutic use
Neoplasm Transplantation
*Olfactory Bulb: SU, surgery
Organ Weight
*Pineal Body: SU, surgery
Prostatic Neoplasms: ME, metabolism
***Prostatic Neoplasms: PA, pathology**
Prostatic Neoplasms: TH, therapy
Rats
Receptors, Androgen: ME, metabolism

RN 73-31-4 (Melatonin); 9007-49-2 (DNA)
CN 0 (Androgens); 0 (Receptors, Androgen)

L20 ANSWER 43 OF 48 CANCERLIT on STN
AN 87215695 CANCERLIT
DN 87215695 PubMed ID: 3555779
TI Biology and therapy of prostatic cancer.
AU Schulze H; Isaacs J T
NC CA 15416 (NCI)
SO CANCER SURVEYS, (1986) 5 (3) 487-503. Ref: 80
Journal code: 8218015. ISSN: 0261-2429.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 87215695
EM 198707
ED Entered STN: 19941107
Last Updated on STN: 19941107
AB There is no effective therapy for increasing the survival of metastatic prostatic cancer. New approaches to this major disease are urgently needed. One approach is to study the biology of prostatic carcinogenesis in order to develop a treatment that prevents the initial development of clinically manifest prostatic cancer. International epidemiological data on the incidence of prostatic cancer and the data on migrant populations make this both possible and practical. For example, it should be possible to lower the incidence of clinical prostatic cancer by more than ten-fold among men in the United States. An alternative approach is to study the tumour biology of prostatic cancer to identify better methods for treating established clinical prostatic cancer. Such studies have already demonstrated that individual prostatic cancers are composed of clones of cancer cells that are phenotypically heterogeneous even before therapy is initiated. Because of this tumour cell heterogeneity, future studies should be directed towards combining androgen ablation plus chemotherapy

and/or radiation early in the disease in order to affect both the **androgen-dependent** and the androgen-independent cancer cells present in individual prostatic cancers.

CT Check Tags: Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Androgen Antagonists: TU, therapeutic use
Combined Modality Therapy
Drug Resistance
Epidemiologic Methods
Prostatic Neoplasms: GE, genetics
Prostatic Neoplasms: PP, physiopathology
Prostatic Neoplasms: PC, prevention & control
***Prostatic Neoplasms: TH, therapy**

CN 0 (Androgen Antagonists)

L20 ANSWER 44 OF 48 CANCERLIT on STN
AN 85116776 CANCERLIT
DN 85116776 PubMed ID: 3918376
TI Management of metastatic prostatic cancer.
AU Paulson D F
SO UROLOGY, (1985 Feb) 25 (2 Suppl) 49-52.
Journal code: 0366151. ISSN: 0090-4295.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 85116776
EM 198503
ED Entered STN: 19941107
Last Updated on STN: 19941107

AB Current management techniques for metastatic prostatic cancer have given rise to controversies regarding the optimal timing, form, and degree of androgen deprivation. Low-dose diethylstilbestrol (DES) or orchiectomy decrease serum testosterone levels while posing less cardiovascular risk than high-dose DES. LH-RH analogues, such as leuprolide or buserelin, also inhibit testosterone production. Some studies suggest that some tumor cells may be relatively, rather than absolutely, **androgen dependent**. This has been the rationale for the combined use of a pure antiandrogen and an LH-RH agonist. Unfortunately, while this combination has been found effective in previously untreated patients, it has not been equally effective in those who have undergone prior therapy and demonstrated disease progression.

CT Check Tags: Human; Male
Adenocarcinoma: DT, drug therapy
*Adenocarcinoma: TH, therapy
Antineoplastic Agents: TU, therapeutic use
Antineoplastic Combined Chemotherapy Protocols: TU, therapeutic use
Buserelin: TU, therapeutic use
Castration
Cyclophosphamide: TU, therapeutic use
Diethylstilbestrol: TU, therapeutic use
Estramustine: TU, therapeutic use
Gonadorelin: AA, analogs & derivatives
Gonadorelin: TU, therapeutic use
Hormones, Synthetic: TU, therapeutic use
Leuprolide
Neoplasm Metastasis
Prostatic Neoplasms: DT, drug therapy
***Prostatic Neoplasms: TH, therapy**

RN 2998-57-4 (Estramustine); 33515-09-2 (Gonadorelin); 50-18-0 (Cyclophosphamide); 53714-56-0 (Leuprolide); 56-53-1 (Diethylstilbestrol); 57982-77-1 (Buserelin)
CN 0 (Antineoplastic Agents); 0 (Antineoplastic Combined Chemotherapy Protocols); 0 (Hormones, Synthetic)

L20 ANSWER 45 OF 48 CANCERLIT on STN
AN 85041652 CANCERLIT
DN 85041652 PubMed ID: 6388093
TI Hormonal therapy: the benefits of postponed initiation.
AU Cockburn A G
SO UROLOGY, (1984 Nov) 24 (5 Suppl) 24-6.
Journal code: 0366151. ISSN: 0090-4295.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 85041652
EM 198412
ED Entered STN: 19941107
Last Updated on STN: 19941107
AB Although the efficacy of antiandrogen therapy is universally recognized in patients with prostatic adenocarcinoma, the dosage and timing of endocrine intervention remain controversial. Deferred anti-androgen therapy is advocated in asymptomatic patients with advanced prostatic cancer, primarily because of the palliative nature of this therapy and the attendant side effects of decreased libido, gynecomastia, or the cardiovascular morbidity associated with estrogen administration. Methodology may soon be available clinically for identification of patients with **androgen-dependent** tumors to maximize the effectiveness of treatment.
CT Check Tags: Human; Male
Adenocarcinoma: DT, drug therapy
*Adenocarcinoma: TH, therapy
*Castration
*Diethylstilbestrol: TU, therapeutic use
Pituitary Hormone-Releasing Hormones: AE, adverse effects
*Pituitary Hormone-Releasing Hormones: TU, therapeutic use
Prostatic Neoplasms: DT, drug therapy
***Prostatic Neoplasms: TH, therapy**
RN 56-53-1 (Diethylstilbestrol)
CN 0 (Pituitary Hormone-Releasing Hormones)

L20 ANSWER 46 OF 48 CANCERLIT on STN
AN 85041651 CANCERLIT
DN 85041651 PubMed ID: 6388092
TI Hormonal therapy in prostatic carcinoma.
AU Resnick M I
SO UROLOGY, (1984 Nov) 24 (5 Suppl) 18-23.
Journal code: 0366151. ISSN: 0090-4295.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 85041651
EM 198412
ED Entered STN: 19941107
Last Updated on STN: 19941107
AB A significant number of patients with newly diagnosed prostatic cancer

will be found to have metastatic disease at time of presentation. Since the work of Huggins and Hodges in the early 1940s, endocrine manipulation and androgen deprivation have become the accepted methods of treating this group of patients. Approximately 70 per cent to 80 per cent of patients demonstrate positive clinical response. Many experience a decrease in the size of the primary tumor, a decrease in the levels of serum acid phosphatase, relief of bone pain, a decrease in bladder outlet obstruction, an increase in appetite, and a generalized improvement in their overall sense of well-being. Adequate hormonal therapy usually consists of estrogen administration of bilateral orchiectomy, but other modalities include administration of antiandrogens, progestational agents, androgen-synthesis inhibitors, and, recently, gonadotropin-releasing hormone analogues. This latter group may have increasing applications, particularly if the evidence indicating reduced side effects continues to be substantiated. The probability of producing a positive clinical response is increased when hormonal therapy is introduced at the time of diagnosis, at which point the tumor is still likely to be **androgen dependent**.

CT Check Tags: Human; Male
Adenocarcinoma: DT, drug therapy
*Adenocarcinoma: TH, therapy
*Androgen Antagonists: TU, therapeutic use
*Castration
Estrogens: AE, adverse effects
*Estrogens: TU, therapeutic use
Pituitary Hormone-Releasing Hormones: TU, therapeutic use
Prostatic Neoplasms: DT, drug therapy
***Prostatic Neoplasms: TH, therapy**

CN 0 (Androgen Antagonists); 0 (Estrogens); 0 (Pituitary Hormone-Releasing Hormones)

L20 ANSWER 47 OF 48 CANCERLIT on STN
AN 84292580 CANCERLIT
DN 84292580 PubMed ID: 6471235
TI The relationship of androgen receptor levels to androgen responsiveness in the Dunning R3327 rat prostate tumor sublines.
AU Diamond D A; Barrack E R
NC AM 22000 (NIADDK)
CA 15416 (NCI)
CA 16924 (NCI)
SO JOURNAL OF UROLOGY, (1984 Oct) 132 (4) 821-7.
Journal code: 0376374. ISSN: 0022-5347.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Abridged Index Medicus Journals; Priority Journals
OS MEDLINE 84292580
EM 198410
ED Entered STN: 19941107
Last Updated on STN: 19941107
AB The objective of this study was to determine whether androgen receptor levels in a transplantable animal model of prostatic adenocarcinoma correlated with androgen responsiveness of the tumor. This is the first comparative study of androgen receptor levels in 3 subcellular compartments (cytosol, nuclear salt-extractable and nuclear salt-resistant fractions) of 4 Dunning R3327 rat prostatic adenocarcinoma sublines that vary in their response to androgen ablation. Tumors were harvested from intact adult male rats in order to best approximate the human clinical setting in which receptor levels are quantitated prior to androgen

ablative therapy. Only the nuclear salt-resistant (nuclear matrix) and total nuclear androgen receptor contents were significantly different among all tumor sublines. The properties of the tumors studied and their nuclear salt-resistant androgen receptor levels were as follows: H tumor--well-differentiated, slow growing, **androgen-dependent**, 63 +/- 11 fmol./mg. DNA; HI tumor--well-differentiated, slow growing, androgen-insensitive, 19 +/- 8 fmol./mg. DNA; G tumor--poorly-differentiated, fast growing, androgen-sensitive, 195 +/- 42 fmol./mg. DNA; and AT-2 tumor--anaplastic, fast growing, androgen-insensitive, no detectable receptors. There was no apparent quantitative relationship between androgen receptor content and tumor growth rates, which varied considerably irrespective of the androgen responsiveness of the tumor. However, there was a qualitative relationship between nuclear salt-resistant or total nuclear receptor content and androgen responsiveness. Higher levels of receptor (H and G tumor sublines) were associated with responsiveness to androgen ablation (cessation or slowing of growth, respectively), whereas lower levels of receptor (HI and AT-2 sublines) were associated with androgen insensitivity. These observations, based on relatively homogeneous tumors, may have important implications for human prostatic cancers which appear to be composed of heterogeneous cell populations.

CT Check Tags: Animal; Male; Support, U.S. Gov't, P.H.S.
*Adenocarcinoma: AN, analysis
Adenocarcinoma: TH, therapy
*Androgens: PD, pharmacology
Cell Nucleus: AN, analysis
Cytosol: AN, analysis
DNA, Neoplasm: AN, analysis
Neoplasm Transplantation
*Neoplasms, Hormone-Dependent: AN, analysis
Neoplasms, Hormone-Dependent: TH, therapy
***Prostatic Neoplasms: AN, analysis**
Prostatic Neoplasms: TH, therapy
Rats
*Receptors, Androgen: AN, analysis
*Receptors, Steroid: AN, analysis
Subcellular Fractions: AN, analysis

CN 0 (Androgens); 0 (DNA, Neoplasm); 0 (Receptors, Androgen); 0 (Receptors, Steroid)

L20 ANSWER 48 OF 48 CANCERLIT on STN
AN 80163589 CANCERLIT
DN 80163589 PubMed ID: 6929004
TI Histology, histochemistry, and acid phosphatase of Noble (Nb) rat prostate adenocarcinomas and treatment of an **androgen-dependent** Nb rat prostate adenocarcinoma.
AU Drago J R; Goldman L B; Maurer R E; Eckels D D; Gershwin M E
SO JOURNAL OF THE NATIONAL CANCER INSTITUTE, (1980 Apr) 64 (4) 931-7. Journal code: 7503089. ISSN: 0027-8874.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 80163589
EM 198006
ED Entered STN: 19990618
Last Updated on STN: 19990618
CT Check Tags: Animal; Male; Support, U.S. Gov't, P.H.S.
*Acid Phosphatase: ME, metabolism

Adenocarcinoma: ME, metabolism
*Adenocarcinoma: PA, pathology
Adenocarcinoma: TH, therapy
Antineoplastic Agents
Castration
Disease Models, Animal
Neoplasms, Experimental: ME, metabolism
Neoplasms, Experimental: PA, pathology
Neoplasms, Experimental: TH, therapy
Prostatic Neoplasms: ME, metabolism
***Prostatic Neoplasms: PA, pathology**
Prostatic Neoplasms: TH, therapy
Rats
CN 0 (Antineoplastic Agents); EC 3.1.3.2 (Acid Phosphatase)

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=> d que l19
L15         31288 SEA FILE=CANCERLIT ABB=ON  PLU=ON  PROSTATIC NEOPLASMS+PFT/CT
L16           720 SEA FILE=CANCERLIT ABB=ON  PLU=ON  L15 AND ANDROGEN INDEPENDENT

L18          3763 SEA FILE=CANCERLIT ABB=ON  PLU=ON  PROSTATIC NEOPLASMS+PFT/CT(L
                  )TH
L19            78 SEA FILE=CANCERLIT ABB=ON  PLU=ON  L18 AND L16


=> d l19 bib ab hitind 1-78

L19  ANSWER 1 OF 78  CANCERLIT on STN
AN   2002196213     CANCERLIT
DN   21958723   PubMed ID: 11961667
TI   Transcription-targeted gene therapy for androgen-
     independent prostate cancer.
AU   Martiniello-Wilks Rosetta; Tsatralis Tania; Russell Peter; Brookes Diana
     E; Zandvliet Dorethea; Lockett Linda J; Both Gerald W; Molloy Peter L;
     Russell Pamela J
CS   Oncology Research Centre, Prince of Wales Hospital, Randwick, New South
     Wales 2031, Australia.. r.martiniello@unsw.edu.au
SO   CANCER GENE THERAPY, (2002 May) 9 (5) 443-52.
     Journal code: 9432230. ISSN: 0929-1903.
CY   England: United Kingdom
DT   Journal; Article; (JOURNAL ARTICLE)
LA   English
FS   MEDLINE; Priority Journals
OS   MEDLINE 2002224783
EM   200210
ED   Entered STN: 20021115
     Last Updated on STN: 20021115
AB   The Escherichia coli enzyme (purine nucleoside phosphorylase, PNP) gene is
     delivered directly into PC3 tumors by one injection of
     replication-deficient human type-5 adenovirus (Ad5). Expressed PNP
     converts the systemically administered prodrug, 6MPDR, to a toxic purine,
     6MP, causing cell death. We sought to increase the specificity of
     recombinant Ad vectors by controlling PNP expression with the promoter
     region from the androgen-dependent, prostate-specific rat probasin (Pb)
     gene. To increase its activity, the promoter was combined with the SV40
     enhancer (SVPb). Cell lines were transfected with plasmids containing both
     a reporter gene, under SVPb control, and a reference gene cassette to
     allow normalization of expression levels. Plasmids expressed approximately
     20-fold more reporter in prostate cancer than in other cells, but
     surprisingly, the SVPb element was both androgen-
     independent and retained substantial prostate specificity. Killing
     by Ad5-SVPb-PNP vector of cell lines cultured with 6MPDR for 6 days was 5-
     to 10-fold greater in prostate cancer than in liver or lung cells. In
     vivo, a single intratumoral injection of Ad5-SVPb-PNP (4 x 10(8) pfu),
     followed by 6MPDR administration twice daily for 6 days, significantly
     suppressed the growth of human prostate tumors in nude mice and increased
     their survival compared to control animals. Thus, the androgen-
     independent, prostate-targeting Ad5 vector reduces human prostate
     cancer growth significantly in vitro and in vivo. This first example of an
     androgen-independent vector points the way toward
     treatment of emerging androgen-independent prostate
     cancer in conjunction with hormone ablation therapy at a time when the
     tumor burden is low.
CT   Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't
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Adenoviridae: GE, genetics
Androgens: PD, pharmacology
*Gene Therapy: MT, methods
Genetic Vectors
Mice
Mice, Nude
Plasmids: ME, metabolism
Prodrugs: PD, pharmacology
***Prostatic Neoplasms: GE, genetics**
***Prostatic Neoplasms: TH, therapy**
Time Factors
Tissue Distribution
*Transcription, Genetic
Transfection
Tumor Cells, Cultured
CN 0 (Androgens); 0 (Genetic Vectors); 0 (Plasmids); 0 (Prodrugs)

L19 ANSWER 2 OF 78 CANCERLIT on STN
AN 2002196001 CANCERLIT
DN 22227740 PubMed ID: 12242725
TI Phase I study of a vaccine using recombinant vaccinia virus expressing PSA (rV-PSA) in patients with metastatic **androgen-independent** prostate cancer.
AU Gulley James; Chen Alice P; Dahut William; Arlen Philip M; Bastian Anne; Steinberg Seth M; Tsang Kwong; Panicali Dennis; Poole Diane; Schlom Jeffrey; Michael Hamilton J
CS Medical Oncology Clinical Research Unit, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, Maryland 20892, USA.
SO PROSTATE, (2002 Oct 1) 53 (2) 109-17.
Journal code: 8101368. ISSN: 0270-4137.
CY United States
DT (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2002480385
EM 200210
ED Entered STN: 20021115
Last Updated on STN: 20021115
AB BACKGROUND: A Phase I trial of recombinant vaccinia prostate specific antigen (rV-PSA) in patients with advanced metastatic prostate cancer was conducted. This report describes 42 patients who were treated with up to three monthly vaccinations. METHODS: All patients were entered on a dose-escalation phase I study of recombinant vaccinia containing the gene for PSA (rV-PSA). The primary objective of this study was to determine the safety of this vaccine in metastatic **androgen-independent** prostate cancer patients. A secondary objective was to assess evidence of anti-tumor activity by PSA measurements, radiologic findings, and immunologic methods. RESULTS: There was no significant treatment-related toxicity apart from erythema, tenderness, and vesicle formation that lasted several days at the site of injection in some patients. There were immunologic responses, in selected patients, as evidenced by an increase in the proportion of PSA-specific T cells after vaccination. Furthermore, we show that these patients' T cells can lyse PSA-expressing tumor cells in vitro. CONCLUSION: Given the low toxicity profile and the evidence of immunologic activity, we believe future study is warranted with PSA-based vaccines in prostate cancer. New PSA-based

vaccines and vaccine strategies are currently being evaluated.
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CT Check Tags: Human; Male
Adenocarcinoma: SC, secondary
*Adenocarcinoma: TH, therapy
Adult
Aged
Aged, 80 and over
Bone Neoplasms: SE, secretion
*Bone Neoplasms: TH, therapy
Cancer Vaccines: AE, adverse effects
Cancer Vaccines: IM, immunology
*Cancer Vaccines: TU, therapeutic use
Disease Progression
*Immunotherapy, Active: MT, methods
Interferon Type II: BL, blood
Middle Age
Prostate-Specific Antigen: GE, genetics
*Prostate-Specific Antigen: IM, immunology
Prostate-Specific Antigen: TU, therapeutic use
Prostatic Neoplasms: IM, immunology
***Prostatic Neoplasms: TH, therapy**
Recombinant Proteins: AE, adverse effects
Recombinant Proteins: IM, immunology
Recombinant Proteins: TU, therapeutic use
Vaccinia virus: GE, genetics
Vaccinia virus: IM, immunology
RN 82115-62-6 (Interferon Type II)
CN 0 (Cancer Vaccines); 0 (Recombinant Proteins); EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 3 OF 78 CANCERLIT on STN
AN 2002193356 CANCERLIT
DN 22215537 PubMed ID: 12228757
TI Controversies surrounding androgen deprivation for prostate cancer.
AU Patterson Stephen G; Balducci Lodovico; Pow-Sang Julio M
CS Genitourinary Oncology Program, H. Lee Moffitt Cancer Center & Research Institute, Tampa, FL 33612, USA.. pattersg@moffitt.usf.edu
SO CANCER CONTROL, (2002 Jul-Aug) 9 (4) 315-25. Ref: 84
Journal code: 9438457. ISSN: 1073-2748.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2002467583
EM 200210
ED Entered STN: 20021115
Last Updated on STN: 20021115
AB BACKGROUND: Management of metastatic prostate cancer continues to evolve. The widespread use of the prostate-specific antigen (PSA) assay has led to earlier diagnosis and earlier detection of recurrent disease. Debates continue regarding the proper use and timing of endocrine therapy with orchiectomy, estrogen agonists, luteinizing hormone-releasing hormone (LHRH) analogs, LHRH antagonists, and androgen antagonists. METHODS: The authors reviewed the significant published materials of the last 20 years that have shaped hormonal management of metastatic and progressive prostate cancer. Major areas of controversy were also identified. RESULTS:

The present approach to hormonal management is summarized. Five potential pathways to the development of **androgen-independent** prostate cancer are described. Controversial topics of hormonal management, including immediate vs delayed hormonal therapy, monotherapy vs maximal androgen blockade (MAB), and intermittent hormonal therapy, are discussed. CONCLUSIONS: Orchiectomy, estrogen agonists, and LHRH analogs have therapeutic equivalence. Patients who have a rising PSA after definitive treatment for prostate cancer and high risk of recurrent disease may warrant early androgen deprivation. MAB does not appear to be significantly better than single-agent LHRH analog therapy. Intermittent therapy may delay emergence of androgen independence and maintain or improve quality of life.

CT Check Tags: Human; Male
Androgen Antagonists: TU, therapeutic use
*Antineoplastic Agents, Hormonal: TU, therapeutic use
Estrogens: AG, agonists
*Gonadorelin
Gonadorelin: AG, agonists
Gonadorelin: AI, antagonists & inhibitors
*Orchiectomy
Orchiectomy: PX, psychology
Prostatic Neoplasms: PX, psychology
***Prostatic Neoplasms: TH, therapy**
Time Factors

RN 33515-09-2 (Gonadorelin)

CN 0 (Androgen Antagonists); 0 (Antineoplastic Agents, Hormonal); 0 (Estrogens)

L19 ANSWER 4 OF 78 CANCERLIT on STN

AN 2002189110 CANCERLIT

DN 22001574 PubMed ID: 12006246

TI Tissue-specific promoters in gene therapy for the treatment of prostate cancer.

AU Shirakawa T; Gotoh A; Wada Y; Kamidono S; Ko S C; Kao C; Gardner T A; Chung L W

CS Department of Urology, Kobe University School of Medicine, Kobe, Japan.. toshiro@kobe-u.ac.jp

SO MOLECULAR UROLOGY, (2000 Summer) 4 (2) 73-82. Ref: 20
Journal code: 9709255. ISSN: 1091-5362.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LA English

FS MEDLINE; Priority Journals

OS MEDLINE 2002264833

EM 200210

ED Entered STN: 20021115
Last Updated on STN: 20021115

AB Delivery of therapeutic toxic genes to and their expression in tumor cells through the use of tissue-specific promoters could decrease their toxic effect on neighboring normal cells when virus-mediated gene delivery results in their infection. We have demonstrated the utility of two prostate cancer-specific promoters, long PSA and osteocalcin, for tissue-specific toxic gene therapy for prostate cancer. The two promoters were highly active in both androgen-dependent and **androgen-independent** prostate cancer cells. We also introduce the Phase I trial of osteocalcin promoter-based toxic gene therapy for bone metastases of prostate cancer, which is in progress at the University of Virginia.

CT Check Tags: Animal; Human; Male
Acyclovir: TU, therapeutic use
Clinical Trials, Phase I
*Gene Therapy
Neoplasm Metastasis
Osteocalcin: GE, genetics
Osteosarcoma: GE, genetics.
Osteosarcoma: TH, therapy
*Promoter Regions (Genetics)
Prostate-Specific Antigen: GE, genetics
***Prostatic Neoplasms: GE, genetics**
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**
RN 104982-03-8 (Osteocalcin); 59277-89-3 (Acyclovir)
CN EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 5 OF 78 CANCERLIT on STN
AN 2002181468 CANCERLIT
DN 22174862 PubMed ID: 12187266
TI CL1-SR39: A noninvasive molecular imaging model of prostate cancer suicide gene therapy using positron emission tomography.
AU Pantuck Allan J; Berger Frank; Zisman Amnon; Nguyen David; Tso Cho Lea; Matherly Jamie; Gambhir Sanjiv S; Belldegrun Arie S
CS Department of Urology, Pharmacology and Crump Institute for Molecular Imaging, University of California School of Medicine, Los Angeles, California, USA.
NC P50 CA86306 (NCI)
R0-1 CA82214 (NCI)
R24 CA92865 (NCI)
SO JOURNAL OF UROLOGY, (2002 Sep) 168 (3) 1193-8.
Journal code: 0376374. ISSN: 0022-5347.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Abridged Index Medicus Journals; Priority Journals
OS MEDLINE 2002437951
EM 200209
ED Entered STN: 20021018
Last Updated on STN: 20021018
AB PURPOSE: We developed a prostate cancer tumor model capable of being noninvasively imaged using positron emission tomography (PET) based on expression of the herpes simplex virus thymidine kinase (HSV1-tk) reporter gene. MATERIALS AND METHODS: The **androgen independent**, metastatic prostate cancer cell lines CL1 and CL1-GFP were stably transfected with the mutant HSV1-tk gene pcDNA3.1/pCMV-sr39tk, which has increased ability to phosphorylate penciclovir. The presence of the sr39tk gene product was analyzed by Western blot analysis and relative thymidine kinase enzyme activity was assessed by a functional thymidine kinase enzyme activity assay. Subcutaneous and orthotopic CL1 and CL1-SR39 tumor xenografts were established in SCID mice. The ability to image CL1-SR39 was assessed using fluorodeoxyglucose and F-penciclovir (F-FHBG) micro-PET (a rodent PET scanner). To investigate the systemic distribution of intratumoral sr39tk injections established CL1 tumors were transiently injected with first generation adenoviral vectors carrying the sr39tk gene under control of the strong cytomegalovirus promoter Ad-CMV-HSV1-sr39tk and imaged using micro-PET. RESULTS: Transfection of sr39tk into CL1 cells was successful. CL1-SR39 thymidine kinase enzyme activity was greater than twice the activity of the glioma cell line C6-SR39 control and above the threshold necessary for micro-PET detection. Fluorodeoxyglucose micro-PET

in SCID mice was positive for CL1 and CL1-SR39 tumors. Selective micro-PET of subcutaneous CL1-SR39 tumors was done using F-FHBG. Micro-PET imaging after systemic and intratumoral injection of Ad-CMV-HSV1-sr39tk revealed significant systemic transgene leakage with significant hepatic expression of sr39TK protein. CONCLUSIONS: Molecular based imaging of sr39tk transfected prostate cancer tumors and adenoviral delivered HSV1-tk suicide gene therapy based on the selective conversion and intracellular trapping of F-FHBG by sr39tk is feasible. Potential applications include noninvasive monitoring of the location, duration and intensity of gene constructs, which may contribute to the safety of clinical gene therapy protocols, and noninvasive imaging of the prostate cancer xenograft response to experimental therapy.

CT Check Tags: Animal; Human; Male; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
*Acyclovir: AA, analogs & derivatives
Acyclovir: DU, diagnostic use
Acyclovir: ME, metabolism
Blotting, Western
Fludeoxyglucose F 18: DU, diagnostic use
*Gene Therapy
Genes, Reporter
Genetic Vectors
Herpesvirus 1, Human: GE, genetics
Mice
Mice, SCID
Neoplasm Transplantation
Prostatic Neoplasms: EN, enzymology
Prostatic Neoplasms: RI, radionuclide imaging
***Prostatic Neoplasms: TH, therapy**
Radiopharmaceuticals
Thymidine Kinase: GE, genetics
Thymidine Kinase: ME, metabolism
*Tomography, Emission-Computed
Transfection
Tumor Cells, Cultured

RN 39809-25-1 (penciclovir); 59277-89-3 (Acyclovir); 63503-12-8 (Fludeoxyglucose F 18)

CN 0 (Genetic Vectors); 0 (Radiopharmaceuticals); EC 2.7.1.21 (Thymidine Kinase)

L19 ANSWER 6 OF 78 CANCERLIT on STN

AN 2002181454 CANCERLIT

DN 22174830 PubMed ID: 12187234

TI Unilateral autonomous testicular testosterone production mimicking **androgen independent** prostate cancer.

AU Lavelle Michael; Schuff Kathyrn G; Keller Frederick S; Binkert Christoph A; O'Hara Michael; Fairfax Cynthia A; Beer Tomasz M

CS Division of Urology, Oregon Health and Science University, Portland, OR, USA.

SO JOURNAL OF UROLOGY, (2002 Sep) 168 (3) 1098-9.
Journal code: 0376374. ISSN: 0022-5347.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS MEDLINE; Abridged Index Medicus Journals; Priority Journals

OS MEDLINE 2002436482

EM 200209

ED Entered STN: 20021018
Last Updated on STN: 20021018

CT Check Tags: Case Report; Human; Male
*Adenocarcinoma: ME, metabolism
Adenocarcinoma: TH, therapy
Antineoplastic Agents, Hormonal: TU, therapeutic use
Diagnosis, Differential
Goserelin: TU, therapeutic use
Middle Age
*Neoplasms, Hormone-Dependent: ME, metabolism
Neoplasms, Hormone-Dependent: TH, therapy
Orchiectomy
Prostatectomy
***Prostatic Neoplasms: ME, metabolism**
Prostatic Neoplasms: TH, therapy
*Testis: ME, metabolism
*Testosterone: BI, biosynthesis
RN 57-85-2 (Testosterone); 65807-02-5 (Goserelin)
CN 0 (Antineoplastic Agents, Hormonal)

L19 ANSWER 7 OF 78 CANCERLIT on STN
AN 2002177963 CANCERLIT
DN 22146611 PubMed ID: 12134144
TI Visualization of advanced human prostate cancer lesions in living mice by a targeted gene transfer vector and optical imaging.
AU Adams Jason Y; Johnson Mai; Sato Makoto; Berger Frank; Gambhir Sanjiv S; Carey Michael; Iruela-Arispe M Luisa; Wu Lily
CS Department of Urology, David Geffen School of Medicine at UCLA, Los Angeles California 90095, USA.
NC P50 CA86306 (NCI)
R0-1 CA82214 (NCI)
R24 CA92865 (NCI)
SO NATURE MEDICINE, (2002 Aug) 8 (8) 891-7.
Journal code: 9502015. ISSN: 1078-8956.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2002402559
EM 200209
ED Entered STN: 20021018
Last Updated on STN: 20021018
AB Non-invasive imaging and transcriptional targeting can improve the safety of therapeutic approaches in cancer. Here we demonstrate the ability to identify metastases in a human-prostate cancer model, employing a prostate-specific adenovirus vector (AdPSE-BC-luc) and a charge-coupled device-imaging system. AdPSE-BC-luc, which expresses firefly luciferase from an enhanced prostate-specific antigen promoter, restricted expression in the liver but produced robust signals in prostate tumors. In fact, expression was higher in advanced, **androgen-independent** tumors than in androgen-dependent lesions. Repetitive imaging over a three-week period after AdPSE-BC-luc injection into tumor-bearing mice revealed that the virus could locate and illuminate metastases in the lung and spine. Systemic injection of low doses of AdPSE-BC-luc illuminated lung metastasis. These results demonstrate the potential use of a non-invasive imaging modality in therapeutic and diagnostic strategies to manage prostate cancer.
CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
*Diagnostic Imaging
*Gene Transfer Techniques

*Genetic Vectors
Liver: ME, metabolism
Liver: PA, pathology
Luciferase: GE, genetics
Luciferase: ME, metabolism
Mice
Mice, SCID
Mice, Transgenic
Neoplasm Transplantation
Prostate-Specific Antigen: ME, metabolism
Prostatic Neoplasms: GE, genetics
***Prostatic Neoplasms: PA, pathology**
Prostatic Neoplasms: TH, therapy
Recombinant Fusion Proteins: GE, genetics
Recombinant Fusion Proteins: ME, metabolism
Spine: PA, pathology
CN 0 (Genetic Vectors); 0 (Recombinant Fusion Proteins); EC 1.13.12.- (Luciferase); EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 8 OF 78 CANCERLIT on STN
AN 2002169825 CANCERLIT
DN 22035382 PubMed ID: 12040457
TI Gene therapy for prostate cancer delivered by ovine adenovirus and mediated by purine nucleoside phosphorylase and fludarabine in mouse models.
AU Voeks D; Martiniello-Wilks R; Madden V; Smith K; Bennetts E; Both G W; Russell P J
CS Oncology Research Centre, Prince of Wales Hospital, Sydney, Australia.
SO GENE THERAPY, (2002 Jun) 9 (12) 759-68.
Journal code: 9421525. ISSN: 0969-7128.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2002298877
EM 200208
ED Entered STN: 20021018
Last Updated on STN: 20021018
AB A gene-directed enzyme pro-drug therapy (GDEPT) based on purine nucleoside phosphorylase (PNP), that converts the prodrug, fludarabine to 2-fluoroadenine, has been described, but studies are limited compared with other GDEPTs. We investigated the in vitro and in vivo efficacies of PNP-GDEPT for treating **androgen-independent** (AI) prostate cancer. The PNP gene controlled by Rous sarcoma virus (RSV) constitutive promoter was delivered using a recombinant ovine adenovirus vector (OAdV220) that uses a different receptor from human adenovirus type 5. In vitro, OAdV220 provided increased transgene expression over a comparable human Ad5 vector in infected AI, murine RM1 prostate cancer cells. Subsequent in vivo testing was therefore confined to OAdV220. Transduction of RM1 cells with OAdV220 before implantation in immunocompetent mice dramatically inhibited subcutaneous (s.c.) tumor growth when fludarabine phosphate was administered systemically and increased mouse survival in a dose-dependent manner. In tumor-bearing C57BL/6 mice, a single intratumoral injection of OAdV220 produced detectable PNP activity for at least 6 days and with prodrug, retarded the growth of aggressive RM1 s.c. tumors by 35% at day 14. There was a consistent trend to reduction of pre-established intraprostatic RM1 tumors. A similar regimen induced significant therapeutic efficacy in human PC3 xenografts. Thus, ovine adenovirus-mediated GDEPT using the PNP

system was effective in vivo against AI prostate cancers, the aggressive murine RM1, and the human PC3 lines. Methods that improve viral dissemination and stimulate the immune system in vivo may further improve efficacy.

CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't
*Adenine: AA, analogs & derivatives
Adenine: TU, therapeutic use
Gene Expression
*Gene Therapy: MT, methods
Genetic Vectors: AD, administration & dosage
Mastadenovirus: GE, genetics
Mice
Mice, Inbred BALB C
Mice, Inbred C57BL
Neoplasms, Experimental: TH, therapy
*Prodrugs: AD, administration & dosage
***Prostatic Neoplasms: TH, therapy**
*Purine-Nucleoside Phosphorylase: GE, genetics
*Sarcoma Viruses, Avian: GE, genetics
Transduction, Genetic: MT, methods
Transplantation, Heterologous
Tumor Cells, Cultured
*Vidarabine Phosphate: AD, administration & dosage
Vidarabine Phosphate: AA, analogs & derivatives

RN 29984-33-6 (Vidarabine Phosphate); 700-49-2 (2-fluoroadenine); 73-24-5 (Adenine); 75607-67-9 (fludarabine monophosphate)

CN 0 (Genetic Vectors); 0 (Prodrugs); EC 2.4.2.1 (Purine-Nucleoside Phosphorylase)

L19 ANSWER 9 OF 78 CANCERLIT on STN
AN 2002169507 CANCERLIT
DN 22091944 PubMed ID: 12097294
TI Expression of the coxsackie adenovirus receptor in normal prostate and in primary and metastatic prostate carcinoma: potential relevance to gene therapy.
AU Rauen Katherine A; Sudilovsky Daniel; Le Jason L; Chew Karen L; Hann Byron; Weinberg Vivian; Schmitt Lars D; McCormick Frank
CS Department of Pediatrics, University of California, San Francisco, California 94115, USA.. rauen@itsa.ucsf.edu
NC P30 CA92193 (NCI)
P50 CA89520 (NCI)
SO CANCER RESEARCH, (2002 Jul 1) 62 (13) 3812-8.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2002359051
EM 200208
ED Entered STN: 20021018
Last Updated on STN: 20021018
AB Adenovirus-based gene therapy may provide an alternative mode of treatment for prostate cancer, especially for late-stage and **androgen-independent** disease for which there is currently no effective treatment. Efficient adenovirus infection of target cells depends upon the presence of the coxsackie adenovirus cell surface receptor, CAR, which is the primary receptor for group C adenoviruses and is important for the attachment of adenovirus to the cell membrane. To evaluate the potential efficacy of adenoviral therapy for prostate cancer, we evaluated CAR

expression in normal prostate tissue and in prostate carcinoma of increasing Gleason grades in paraffin-embedded, archival tissues using a polyclonal antibody raised against human CAR. Immunohistochemical analysis of benign prostate epithelia demonstrated intense luminal and lateral cell membrane staining. There was a statistically significant difference in CAR membrane expression with respect to Gleason score. In addition, metastatic prostate specimens demonstrated strong membrane staining for CAR. Adenovirus therapy may, therefore, provide an alternate modality in the treatment of prostate cancer and may be especially efficacious in the treatment of metastatic disease.

CT Check Tags: Animal; Human; Male; Support, U.S. Gov't, P.H.S.
Adult
Aged
Bone Neoplasms: ME, metabolism
Bone Neoplasms: SC, secondary
CHO Cells
*Gene Therapy
Hamsters
Immunohistochemistry
Middle Age
Prostate: ME, metabolism
***Prostatic Neoplasms: ME, metabolism**
Prostatic Neoplasms: PA, pathology
Prostatic Neoplasms: TH, therapy
*Receptors, Virus: BI, biosynthesis

CN 0 (CAR receptor); 0 (Receptors, Virus)

L19 ANSWER 10 OF 78 CANCERLIT on STN
AN 2002162052 CANCERLIT
DN 22032765 PubMed ID: 12036918
TI A novel targeting modality to enhance adenoviral replication by vitamin D(3) in **androgen-independent** human prostate cancer cells and tumors.
AU Hsieh Chia-Ling; Yang Ling; Miao Li; Yeung Fang; Kao Chinghai; Yang Hua; Zhau Haiyen E; Chung Leland W K
CS Department of Urology, Molecular Urology and Therapeutics Program, Emory University School of Medicine, Atlanta, GA 30322, USA.. chsieh2@emory.edu
NC CA 85555 (NCI)
SO CANCER RESEARCH, (2002 Jun 1) 62 (11) 3084-92.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2002296386
EM 200207
ED Entered STN: 20020819
Last Updated on STN: 20020819
AB We report the development of a novel replication-competent adenoviral vector, Ad-hOC-E1, containing a single bidirectional human osteocalcin (hOC) promoter to drive both the early viral E1A and E1B gene. This vector selectively replicated in OC-expressing but not non-OC-expressing cells, with viral replication enhanced at least 10-fold on vitamin D(3) exposure. Both the artificial TATA-box and hOC promoter element in this bidirectional promoter construct were controlled by a common OC regulatory element which selectively activated OC expression in cells. The expression ofE1A and E1B gene by Ad-hOC-E1 can be markedly induced by vitamin D(3). Unlike Ad-sPSA-E1, an adenoviral vector with viral replication controlled by a strong super prostate-specific antigen (sPSA) promoter which only

replicates in PSA-expressing cells with androgen receptor (AR), Ad-hOC-E1 retarded the growth of both androgen-dependent and **androgen-independent** prostate cancer cells irrespective of their basal level of AR and PSA expression. A single i.v. administration of 2 x 10(9) plaque-forming units of Ad-hOC-E1 inhibited the growth of previously established s.c. DU145 tumors (an AR- and PSA-negative cell line). Viral replication is highly enhanced by i.p. administration of vitamin D(3). Ultimately, enhancing Ad-hOC-E1 viral replication by vitamin D(3) may be used clinically to treat localized and osseous metastatic prostate cancer in men.

CT Check Tags: Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
Adenoviridae: DE, drug effects
Adenoviridae: GE, genetics
*Adenoviridae: PH, physiology
Adenovirus E1A Proteins: BI, biosynthesis
Adenovirus E1A Proteins: GE, genetics
Adenovirus E1B Proteins: BI, biosynthesis
Adenovirus E1B Proteins: GE, genetics
Cell Division: GE, genetics
*Cholecalciferol: PD, pharmacology
*Gene Therapy: MT, methods
Genetic Vectors: GE, genetics
Osteocalcin: BI, biosynthesis
Osteocalcin: GE, genetics
Prostatic Neoplasms: ME, metabolism
Prostatic Neoplasms: PA, pathology
Prostatic Neoplasms: TH, therapy
***Prostatic Neoplasms: VI, virology**
RNA, Messenger: BI, biosynthesis
RNA, Messenger: GE, genetics
Up-Regulation
*Virus Replication: DE, drug effects

RN 104982-03-8 (Osteocalcin); 67-97-0 (Cholecalciferol)

CN 0 (Adenovirus E1A Proteins); 0 (Adenovirus E1B Proteins); 0 (Genetic Vectors); 0 (RNA, Messenger)

L19 ANSWER 11 OF 78 CANCERLIT on STN

AN 2002161314 CANCERLIT

DN 21541205 PubMed ID: 11684838

TI Molecular biology of the androgen receptor: from molecular understanding to the clinic.

AU Eder I E; Culig Z; Putz T; Nessler-Menardi C; Bartsch G; Klocker H

CS Department of Urology, University of Innsbruck, Austria.

SO EUROPEAN UROLOGY, (2001 Sep) 40 (3) 241-51. Ref: 122
Journal code: 7512719. ISSN: 0302-2838.

CY Netherlands

DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LA English

FS MEDLINE; Priority Journals

OS MEDLINE 2001610216

EM 200207

ED Entered STN: 20020819
Last Updated on STN: 20020819

AB The androgen receptor (AR) is the key regulatory element of androgen signaling in the cell. It mediates action of androgens and is therefore essential for growth, function and differentiation of the human male

urogenital tract. Genetic alterations in the AR gene may cause impaired development resulting in androgen insensitivity syndromes (AIS) or in neurodegenerative diseases like Kennedy syndrome. Besides the crucial role in the process of virilization during embryogenesis and puberty, the AR also plays an important role in the adult man as the intracellular mediator of androgen action. Androgen withdrawal and/or AR blockade is the main choice of treatment of nonorgan-confined prostate cancer. Unfortunately, this treatment is only palliative and a majority of these tumors recur and progress to an **androgen-independent** and therapy-resistant stage. Recent findings gave new insight into the molecular structure and function of the AR and improved our understanding about prostate cancer progression, consequently resulting in the development of novel treatments. It has become evident that the AR is a nuclear transcription factor that can be activated ligand-dependently by androgens as well as ligand-independently by other hormones and various growth factors, respectively. Moreover, it was shown that the interaction of the AR with other proteins of the intracellular signal transduction cascade may promote prostate tumor growth. This review will summarize the most important findings about the AR and the androgen signaling pathway to improve the understanding of prostate diseases and novel treatment strategies that may be useful in the clinic.

CT Check Tags: Human; Male; Support, Non-U.S. Gov't
Androgen-Insensitivity Syndrome: GE, genetics
Point Mutation
***Prostatic Neoplasms: GE, genetics**
Prostatic Neoplasms: TH, therapy
*Receptors, Androgen: GE, genetics
Terminal Repeat Sequences

CN 0 (Receptors, Androgen)

L19 ANSWER 12 OF 78 CANCERLIT on STN
AN 2002158613 CANCERLIT
DN 21892800 PubMed ID: 11895908
TI The association of p21((WAF-1/CIP1)) with progression to **androgen-independent** prostate cancer.
AU Fizazi Karim; Martinez Luis A; Sikes Charles R; Johnston Dennis A; Stephens L Clifton; McDonnell Timothy J; Logothetis Christopher J; Trapman Jon; Pisters Louis L; Ordonez Nelson G; Troncoso Patricia; Navone Nora M
CS Department of Genitourinary Medical Oncology, The University of Texas M. D. Anderson Cancer Center, Houston, Texas 77030, USA.
NC CA 75499 (NCI)
SO CLINICAL CANCER RESEARCH, (2002 Mar) 8 (3) 775-81.
Journal code: 9502500. ISSN: 1078-0432.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2002178467
EM 200207
ED Entered STN: 20020819
Last Updated on STN: 20020819
AB The molecular events leading to progression toward **androgen-independent** prostate cancer (AIPC) are not fully understood. The p21((WAF-1/CIP1)) (p21) gene has been identified as a key factor for the regulation of cell growth. The expression of p21 was examined by immunohistochemical studies in 105 prostate cancer samples: (a) 7 of 30 (23%) androgen-dependent tumors; and (b) 36 of 75 (48%) **androgen-independent** tumors stained positive for p21 ($P < 0.02$). No association was found between p21 expression and p53, bcl-2, and the

androgen receptor protein expression in bone metastases of patients with AIPC, whereas there was a significant association with a high Ki-67 index ($P < 0.05$). In 4 of 43 (9%) cases, tumors displayed a p53-negative, bcl-2-negative, and p21-positive phenotype. A xenograft mouse model of prostate cancer using the androgen-responsive MDA PCa 2b prostate cancer cell line was used to study p21 expression after androgen deprivation and at relapse. Androgen deprivation reduced p21 expression to undetectable levels after 14 days. Tumor relapse, defining AIPC, was associated with increased expression of p21 to levels comparable with those found before castration. In this model, p21 expression at relapse was also correlated with a high Ki-67 index. In conclusion, p21 expression is associated with the progression to AIPC. A possible explanation involves a paracrine effect of p21 mediated by the release of mitogenic and antiapoptotic factors. Another explanation involves the regulation of p21 expression by the androgen receptor, which also suggests that p21 may have antiapoptotic function in prostate cancer.

CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Androgens: PD, pharmacology
Biopsy
Bone Neoplasms: ME, metabolism
Bone Neoplasms: PA, pathology
Bone Neoplasms: SC, secondary
Cyclins: GE, genetics
*Cyclins: ME, metabolism
Disease Progression
*Gene Expression Regulation, Neoplastic: GE, genetics
Immunoenzyme Techniques
Ki-67 Antigen: ME, metabolism
Mice
Mice, Nude
Neoplasm Recurrence, Local: ME, metabolism
Neoplasm Recurrence, Local: PA, pathology
Neoplasm Staging
Neoplasms, Experimental: ME, metabolism
Neoplasms, Experimental: PA, pathology
***Prostatic Neoplasms: ME, metabolism**
Prostatic Neoplasms: PA, pathology
Prostatic Neoplasms: TH, therapy
Protein p53: ME, metabolism
Proto-Oncogene Proteins c-bcl-2: ME, metabolism

CN 0 (Androgens); 0 (Cip1 protein); 0 (Cyclins); 0 (Ki-67 Antigen); 0 (Protein p53); 0 (Proto-Oncogene Proteins c-bcl-2)

L19 ANSWER 13 OF 78 CANCERLIT on STN
AN 2002154886 CANCERLIT
DN 22035582 PubMed ID: 12039928
TI Salvage cryotherapy for recurrent prostate cancer after radiotherapy: variables affecting patient outcome.
AU Izawa Jonathan I; Madsen Lydia T; Scott Shellie M; Tran Jean-Paul; McGuire Edward J; Von Eschenbach Andrew C; Pisters Louis L
CS Department of Urology, University of Texas M.D. Anderson Cancer Center, Houston, TX 77030, USA.
NC CA16672 (NCI)
SO JOURNAL OF CLINICAL ONCOLOGY, (2002 Jun 1) 20 (11) 2664-71. Journal code: 8309333. ISSN: 0732-183X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English

FS MEDLINE; Priority Journals
OS MEDLINE 2002299044
EM 200206
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB PURPOSE: To determine the long-term disease-specific survival (DSS) and disease-free survival (DFS) rates after salvage cryotherapy for locally recurrent adenocarcinoma of the prostate and to identify pretreatment factors that have an impact on DSS and DFS. PATIENTS AND METHODS: Between July 1992 and January 1995, 131 patients who had received definitive radiation therapy (XRT) underwent salvage cryotherapy for locally recurrent adenocarcinoma of the prostate. Cryotherapy failure was defined as an increasing postcryotherapy prostate-specific antigen (PSA) level of > or = 2 ng/mL above the postcryotherapy nadir, a positive prostate biopsy, or radiographic evidence of metastatic disease. Clinical variables were studied to determine whether there was an association with the DSS and DFS. RESULTS: The median follow-up was 4.8 years. The 5-year DSS rates were 87% for patients with a precryotherapy Gleason score < or = 8 and 63% for those with Gleason scores of 9 and 10 (P =.012). The 5-year DFS rates were 57% for patients with a precryotherapy PSA level of < or = 10 ng/mL and 23% for those with a PSA level greater than 10 ng/mL (P =.0004). The 5-year DSS rates for patients with a pre-XRT clinical stage of T1 to T2 and those with a clinical stage of T3 to T4 were 94% and 72%, respectively (P =.0041). The 5-year DFS rates for these groups were 90% and 69%, respectively (P =.0057). CONCLUSION: **Androgen-independent** local recurrences, Gleason score, and pre-XRT clinical stage were important factors that had an impact on DSS and DFS. The subset of patients cured by salvage cryotherapy seems to be small, and patient selection is important.
CT Check Tags: Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Adenocarcinoma: MO, mortality
Adenocarcinoma: PA, pathology
Adenocarcinoma: RT, radiotherapy
*Adenocarcinoma: TH, therapy
*Cryotherapy
Disease-Free Survival
Neoplasm Recurrence, Local: MO, mortality
Neoplasm Recurrence, Local: PA, pathology
*Neoplasm Recurrence, Local: TH, therapy
Prostatic Neoplasms: MO, mortality
Prostatic Neoplasms: PA, pathology
Prostatic Neoplasms: RT, radiotherapy
***Prostatic Neoplasms: TH, therapy**
Retrospective Studies
*Salvage Therapy
Survival Rate

L19 ANSWER 14 OF 78 CANCERLIT on STN
AN 2002148190 CANCERLIT
DN 21669665 PubMed ID: 11805477
TI Diagnosing and treating small-cell carcinomas of prostatic origin.
AU Spieth Michael E; Lin Y Gregory; Nguyen Thanhcuong T
CS Department of Radiology, Marshfield Clinic, Wisconsin 54449, USA.. spiethm@mfldclin.edu
SO CLINICAL NUCLEAR MEDICINE, (2002 Jan) 27 (1) 11-7.
Journal code: 7611109. ISSN: 0363-9762.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2002084032
EM 200205
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB PURPOSE: Small-cell carcinoma is very aggressive, metastasizes early and often, and does not respond to most chemotherapy regimens. In approximately 50% of cases of prostate cancer, tumors are a combination of small-cell carcinoma and androgen-sensitive adenocarcinoma. It is widely believed that no successful treatment exists for **androgen-independent** prostate cancer. METHODS: A 67-year-old man had undergone androgen ablation therapy and radical prostatectomy for prostate cancer followed by bilateral orchiectomy, limited radiation therapy, and unsuccessful chemotherapy for pain-causing metastatic bone disease. Biopsy and immunohistochemical analysis revealed neuroendocrine differentiation of the cancer. The full extent of metastatic disease was assessed successfully using In-111, a somatostatin derivative. Octreotide acetate was used to treat the tumors. RESULTS: In-111 OctreoScan scintigraphy was more sensitive in the diagnostic demonstration of metastatic foci than was bone scanning. Therapy with the cold somatostatin derivative resulted in a rapid and significant relief of pain with significant tumor shrinkage. The patient remained in remission for at least 10 weeks, when he was lost to follow-up. CONCLUSIONS: Somatostatin analogs and their radionuclide and cytotoxic derivatives are recommended as adjuvant treatments for prostate carcinoma, especially in those patients who are at high risk for carcinoma recurrence after radical prostatectomy and who have advanced prostate carcinoma at the time of relapse. Because small-cell carcinomas of the prostate and lung are identical, these analogs may be useful in the detection and treatment of these tumors as well.
CT Check Tags: Case Report; Comparative Study; Human; Male
Aged
Antineoplastic Combined Chemotherapy Protocols: TU, therapeutic use
*Carcinoma, Small Cell: DI, diagnosis
Carcinoma, Small Cell: SC, secondary
*Carcinoma, Small Cell: TH, therapy
Follow-Up Studies
Lung Neoplasms: DI, diagnosis
Lung Neoplasms: SC, secondary
Lung Neoplasms: TH, therapy
Magnetic Resonance Imaging
Prostatectomy
***Prostatic Neoplasms: DI, diagnosis**
***Prostatic Neoplasms: TH, therapy**
Radiotherapy, Adjuvant
Somatostatin: AD, administration & dosage
Somatostatin: AA, analogs & derivatives
Treatment Outcome
RN 51110-01-1 (Somatostatin)
CN 0 (Antineoplastic Combined Chemotherapy Protocols)

L19 ANSWER 15 OF 78 CANCERLIT on STN
AN 2002132525 CANCERLIT
DN 21899511 PubMed ID: 11901478
TI New discoveries in prostate cancer biology and treatment. 5-9 December 2001, Naples, Florida, USA.
AU Cooper Carlton R; Chay Christopher H; Pienta Kenneth J
CS University of Michigan Comprehensive Cancer Center, Department of Internal Medicine, Division of Haematology/Oncology and Department of Urology, Ann

Arbor, MI 48109, USA.
SO Expert Opin Ther Targets, (2002 Feb) 6 (1) 123-7.
Journal code: 101127833. ISSN: 1472-8222.
CY England: United Kingdom
DT Conference; Conference Article; (CONGRESSES)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2002171109
EM 200204
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB Androgen independence and bone metastasis are lethal complications in patients with advanced prostate cancer. Presently, there is no cure for patients with **androgen-independent** prostate cancer. In order to develop more effective therapies for this disease, the molecular events involved in the development of androgen independence and bone metastasis must be elucidated and then targeted by therapeutic agents. Several studies presented at a recent conference on prostate cancer sponsored by the American Association for Cancer Research (AACR) provided evidence that prostate cancer metastasis to bone is mediated by the prostate cancer cell expression of molecules that allow the cells to invade, grow in and stimulate cells in the bone microenvironment resulting in an osteoblastic reaction. Androgen independence was reportedly mediated by an increased expression of survival genes following androgen ablation therapies and several molecular mechanisms involved in genetic instability. Treatment strategies are being designed to target some of the molecular events involved in androgen independence and bone metastasis. Targeting these molecular events with combinational therapies will hopefully delay the progression to androgen independence in patients with early stage disease, suppress the growth of **androgen-independent** cells in patients with advanced disease and enhance the chemosensitivity of **androgen-independent** cells.
CT Check Tags: Human; Male
Antineoplastic Agents: TU, therapeutic use
Prostatic Neoplasms: DT, drug therapy
Prostatic Neoplasms: GE, genetics
***Prostatic Neoplasms: PA, pathology**
***Prostatic Neoplasms: TH, therapy**
CN 0 (Antineoplastic Agents)

L19 ANSWER 16 OF 78 CANCERLIT on STN
AN 2002130780 CANCERLIT
DN 21896923 PubMed ID: 11900250
TI The development of **androgen-independent** prostate cancer.
AU Feldman B J; Feldman D
CS Department of Medicine, Stanford University School of Medicine, California 94305-5103, USA.. feldman@cmgm.stanford.edu
SO Nat Rev Cancer, (2001 Oct) 1 (1) 34-45. Ref: 95
Journal code: 101124168. ISSN: 1474-175X.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2002168724
EM 200204
ED Entered STN: 20020726

Last Updated on STN: 20020819
AB The normal prostate and early-stage prostate cancers depend on androgens for growth and survival, and androgen ablation therapy causes them to regress. Cancers that are not cured by surgery eventually become **androgen independent**, rendering anti-androgen therapy ineffective. But how does androgen independence arise? We predict that understanding the pathways that lead to the development of **androgen-independent** prostate cancer will pave the way to effective therapies for these, at present, untreatable cancers.
CT Check Tags: Human; Male
Androgens: AN, analysis
*Androgens: PH, physiology
Growth Substances: PH, physiology
Mutation
***Prostatic Neoplasms: ET, etiology**
Prostatic Neoplasms: TH, therapy
Receptor Protein-Tyrosine Kinases: PH, physiology
Receptors, Androgen: GE, genetics
Receptors, Androgen: PH, physiology
CN 0 (Androgens); 0 (Growth Substances); 0 (Receptors, Androgen); EC 2.7.11.- (Receptor Protein-Tyrosine Kinases)

L19 ANSWER 17 OF 78 CANCERLIT on STN
AN 2002120419 CANCERLIT
DN 21596293 PubMed ID: 11760786
TI Expression, specificity and immunotherapy potential of prostate-associated genes in murine cell lines.
AU Grossmann M E; Wood M; Celis E
CS Department of Urology, Mayo Clinic, Rochester, MN 55905, USA.. grossmann.michael@mayo.edu
NC CA09127 (NCI)
R01CA82677 (NCI)
SO WORLD JOURNAL OF UROLOGY, (2001 Nov) 19 (5) 365-70.
Journal code: 8307716. ISSN: 0724-4983.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2002032792
EM 200202
ED Entered STN: 20020726
Last Updated on STN: 20021018
AB The TRAMP-C1 (C1) and TRAMP-C2 (C2) cell lines were derived from a prostate tumor that arose in a mouse from the transgenic adenocarcinoma mouse prostate (TRAMP) model. However, their similarity to primary prostate tumors and therefore their usefulness in immunotherapy studies has not been clearly defined. We showed using RT-PCR that these cell lines exhibited a variety of prostate-specific genes expressed by human prostate tumors that may be used as tumor-associated antigens for immunotherapy. Interestingly, several of these genes are also expressed in cell lines that are not prostatic in origin. The prostate cell lines were also shown to grow in an **androgen-independent** manner, to be capable of expressing MHC class I and to be susceptible to specific lysis by cytotoxic T lymphocytes. Therefore, these cell lines will provide us with the ability to evaluate immune responses to and tolerance of prostate-specific protein peptides in an animal model.
CT Check Tags: Animal; In Vitro; Male; Support, U.S. Gov't, P.H.S.
*Adenocarcinoma: GE, genetics
Adenocarcinoma: IM, immunology

*Adenocarcinoma: TH, therapy
*Antibody Specificity: GE, genetics
Antibody Specificity: IM, immunology
Antigens, Neoplasm: GE, genetics
Antigens, Neoplasm: IM, immunology
Carboxypeptidases: GE, genetics
Carboxypeptidases: IM, immunology
Disease Models, Animal
*Gene Expression: GE, genetics
Gene Expression: IM, immunology
Genes, Tumor Suppressor: PH, physiology
Homeodomain Proteins: GE, genetics
Homeodomain Proteins: IM, immunology
*Immunotherapy
Membrane Glycoproteins: GE, genetics
Membrane Glycoproteins: IM, immunology
Mice
Mice, Transgenic
Neoplasm Proteins: GE, genetics
Neoplasm Proteins: IM, immunology
***Prostatic Neoplasms: GE, genetics**
Prostatic Neoplasms: IM, immunology
***Prostatic Neoplasms: TH, therapy**
Prostatic Secretory Proteins: GE, genetics
Prostatic Secretory Proteins: IM, immunology
Protein-Tyrosine-Phosphatase: GE, genetics
Protein-Tyrosine-Phosphatase: IM, immunology
Reverse Transcriptase Polymerase Chain Reaction
Transcription Factors: GE, genetics
Transcription Factors: IM, immunology
*Tumor Cells, Cultured: PH, physiology

CN 0 (Antigens, Neoplasm); 0 (Homeodomain Proteins); 0 (Hoxb-13 protein); 0 (Membrane Glycoproteins); 0 (Neoplasm Proteins); 0 (Nkx-3.1 protein); 0 (Prostatic Secretory Proteins); 0 (Transcription Factors); 0 (prostate stem cell antigen); EC 3.1.3.- (prostatic acid phosphatase); EC 3.1.3.48 (Protein-Tyrosine-Phosphatase); EC 3.4.- (Carboxypeptidases); EC 3.4.17.21 (glutamate carboxypeptidase II)

L19 ANSWER 18 OF 78 CANCERLIT on STN
AN 2002117191 CANCERLIT
DN 21611904 PubMed ID: 11745692
TI Expression of basal cell keratins in human prostate cancer metastases and cell lines.
AU van Leenders G J; Aalders T W; Hulsbergen-van de Kaa C A; Ruiter D J; Schalken J A
CS Department of Pathology, University Medical Centre St. Radboud, Nijmegen, The Netherlands.. G.vanleenders@pathol.azn.nl
SO JOURNAL OF PATHOLOGY, (2001 Dec) 195 (5) 563-70.
Journal code: 0204634. ISSN: 0022-3417.
CY England: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2001698431
EM 200202
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB Within normal human prostate epithelium, basal and luminal cells can be discriminated by their expression of keratins (K). While basal cells

express K5/14, luminal cells show expression of K8/18 and an intermediate cell population can be identified by co-expression of K5/18. Prostate cancer is predominantly composed of luminal and neuroendocrine cells, while a minority of cells have a basal phenotype. In order to distinguish between basal and intermediate cells, and to assess the effects of androgen deprivation on prostate cancer, 56 human prostate cancer metastases and three cancer cell lines were characterized using antibodies to K5, K14, K18, and the neuroendocrine marker chromogranin A (ChA). The staining was performed on paraffin tissue and visualized by the avidin-biotin-peroxidase complex method. Protein expression was quantified as the number of positive cells in 20 high power fields (HPF; 400x). Keratin expression in the prostate cancer cell lines LNCaP, DU145, and PC3 was analysed by immunofluorescence with triple staining and confocal laser scanning microscopy. Prostate cancer metastases were consistently positive for K18 and negative for K14, irrespective of hormonal therapy. K5 expression was displayed in 28.9% of the tumours without treatment, in 75% after androgen deprivation, and in 57.1% of hormone-escaped prostate carcinomas. After androgen deprivation, the number of K5-expressing cells increased significantly. While androgen-dependent prostate cancer showed a median of 0 cells/20 HPF (range 0-50), regressed tumours displayed 22.5 (range 0-65) and hormone-escaped tumours 7.5 (range 0-361) positive cells/20 HPF. Expression of ChA was observed in 47.4% of the androgen-dependent tumours. The number of neuroendocrine cells was not significantly affected in regressed or hormone-escaped disease. The androgen-dependent cell line LNCaP stained for K18, while the **androgen-independent** lines DU145 and PC3 both expressed K5 and 18. Expression of K5 in the absence of K14 identifies the existence of an intermediate cell population in prostate carcinoma. Accumulation of intermediate cells in regressed and hormone-escaped prostate cancer indicates that for their survival, these cells are **androgen-independent**.

CT Check Tags: Human; Male
Adenocarcinoma: ME, metabolism
*Adenocarcinoma: SC, secondary
Adenocarcinoma: TH, therapy
Chromogranins: ME, metabolism
Immunoenzyme Techniques
*Keratin: ME, metabolism
*Neoplasm Proteins: ME, metabolism
***Prostatic Neoplasms: ME, metabolism**
Prostatic Neoplasms: TH, therapy
Tumor Cells, Cultured
*Tumor Markers, Biological: ME, metabolism

RN 68238-35-7 (Keratin)

CN 0 (Chromogranins); 0 (Neoplasm Proteins); 0 (Tumor Markers, Biological); 0 (chromogranin A); 0 (keratin 5)

L19 ANSWER 19 OF 78 CANCERLIT on STN

AN 2002115739 CANCERLIT

DN 21655866 PubMed ID: 11796285

TI Nadir prostate-specific antigen as a predictor of progression to **androgen-independent** prostate cancer.

AU Benaim Elie A; Pace Christopher M; Lam Po M; Roehrborn Claus G

CS Department of Urology, University of Texas Southwestern Medical Center at Dallas and North Texas Veterans Affairs Health Care Center, Dallas, Texas 75390-9110, USA.

SO UROLOGY, (2002 Jan) 59 (1) 73-8.
Journal code: 0366151. ISSN: 1527-9995.

CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2002071056
EM 200202
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB OBJECTIVES: To determine the value of the before and after treatment level of prostate-specific antigen (PSA) to predict the time to **androgen -independent** progression (AIP) in patients with advanced prostate cancer who received androgen-deprivation therapy (ADT) at the time of recurrence or progression. METHODS: The records of 153 patients with advanced or metastatic prostate cancer who were treated with ADT were retrospectively reviewed. Fifty-six percent of the patients were initially treated with ADT. In the remainder, ADT was started at progression and/or failure. AIP was defined as two consecutive elevations of serum PSA above the nadir value by any threshold. Kaplan-Meier and multiple logistic regression analyses were used to determine the potential predictors of AIP. RESULTS: The median duration of the PSA response was 24 months. The most important predictors of the time to AIP were the initial Gleason grade and the nadir PSA level after the initiation of ADT. The odds ratio of having a response greater than 24 months was 15-times higher in patients achieving an undetectable serum PSA level versus those who did not. For each point increase in the Gleason sum, patients had a five times higher chance of progressing to AIP in 24 months or less. CONCLUSIONS: The ability to achieve an undetectable nadir PSA level and the initial Gleason grade are significant predictors of the time to AIP in men treated with ADT for metastatic and advanced prostate cancer.
CT Check Tags: Human; Male
Aged
Androgen Antagonists: TU, therapeutic use
Disease Progression
Gonadorelin: AA, analogs & derivatives
Odds Ratio
Orchiectomy
*Prostate-Specific Antigen: BL, blood
***Prostatic Neoplasms: BL, blood**
Prostatic Neoplasms: PA, pathology
Prostatic Neoplasms: TH, therapy
Retrospective Studies
Time Factors
RN 33515-09-2 (Gonadorelin)
CN 0 (Androgen Antagonists); EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 20 OF 78 CANCERLIT on STN
AN 2002107713 CANCERLIT
DN 21608167 PubMed ID: 11743353
TI Enhanced transgene expression in **androgen independent** prostate cancer gene therapy by taxane chemotherapeutic agents.
AU Li Yingming; Okegawa Takatsugu; Lombardi Donald P; Frenkel Eugene P; Hsieh Jer-Tsong
CS Department of Urology, University of Texas Southwestern Medical Center, 5323 Harry Hines Blvd., Dallas, TX 75390-9110, USA.
NC R01 CA 73017 (NCI)
SO JOURNAL OF UROLOGY, (2002 Jan) 167 (1) 339-46.
Journal code: 0376374. ISSN: 0022-5347.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS MEDLINE; Abridged Index Medicus Journals; Priority Journals
OS MEDLINE 2001697522
EM 200201
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB PURPOSE: Chemotherapy is often used as a primary therapy for metastatic cancer because it kills cells en masse. However, high doses of chemotherapeutic drugs can cause toxicity in nontarget organs. Gene therapy may provide a better alternative to chemotherapy because its targeting of specific genes may reduce the undesirable toxicity associated with chemotherapy. We evaluated whether the chemotherapeutic agent docetaxel or paclitaxel may be combined with gene therapy to create a new therapeutic regimen for metastatic **androgen independent** prostate cancer. MATERIALS AND METHODS: The 2 **androgen independent** prostate cancer cell lines PC-3 and DU 145 were treated with docetaxel or paclitaxel. Three recombinant adenoviruses containing p21WAF-1/CIP1, p53 protein or beta-galactosidase complementary DNA under the control of cytomegalovirus promoter were used to determine transgene expression. They were evaluated by Western blot analysis, beta-galactosidase activity or in vitro growth assays. The [(3)H] labeled E1 deleted adenovirus dl312 was used to determine adenovirus uptake into cells. RESULTS: Docetaxel and paclitaxel enhanced adenovirus mediated transgene expression. Docetaxel appears to be a more potent growth inhibitor in vitro. Elevated transgene expression in virus infected cells induced by these 2 drugs was produced by increased cytomegalovirus promoter activity rather than increased virus uptake. CONCLUSIONS: The potential synergy of gene therapy with docetaxel and paclitaxel may be an important direction for future therapy for metastatic **androgen independent** prostate cancer.
CT Check Tags: Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Adenoviridae: GE, genetics
*Antineoplastic Agents, Phytogenic: PD, pharmacology
Antineoplastic Agents, Phytogenic: TU, therapeutic use
Gene Expression: DE, drug effects
*Gene Therapy: MT, methods
*Paclitaxel: AA, analogs & derivatives
*Paclitaxel: PD, pharmacology
Paclitaxel: TU, therapeutic use
Prostatic Neoplasms: GE, genetics
***Prostatic Neoplasms: TH, therapy**
*Transgenes
Tumor Cells, Cultured
RN 114977-28-5 (docetaxel); 33069-62-4 (Paclitaxel)
CN 0 (Antineoplastic Agents, Phytogenic)

L19 ANSWER 21 OF 78 CANCERLIT on STN
AN 2002089066 CANCERLIT
DN 21490851 PubMed ID: 11605036
TI Up-regulation of neuroendocrine differentiation in prostate cancer after androgen deprivation therapy, degree and androgen independence.
AU Ito T; Yamamoto S; Ohno Y; Namiki K; Aizawa T; Akiyama A; Tachibana M
CS Department of Urology, Tokyo Medical University, Tokyo, Japan. takaaki-med.ac.jp.
SO ONCOLOGY REPORTS, (2001 Nov-Dec) 8 (6) 1221-4.
Journal code: 9422756. ISSN: 1021-335X.
CY Greece
DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2001558294
EM 200112
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB The up-regulation of neuroendocrine (NE) differentiation after hormonal therapy, as well as the relationship between the degree of NE differentiation and androgen independence was investigated. One hundred and thirty-seven whole prostate specimens that were derived from surgery and autopsy (group A: no hormonal therapy, 44 patients; group B: with hormonal therapy less than 12 months, 25 patients; group C: with hormonal therapy more than 13 months, 68 patients) were studied. Neuroendocrine differentiation was evaluated by immunostaining with chromogranin A. The degree of NE differentiation was evaluated by the percentage area of positive NE cell expression (grade 0, negative; grade 1, 1-33%; grade 2, 34-66%; grade 3, 67-100%). The degree of NE differentiation was compared in **androgen-independent** and -dependent tumors in group C. Neuroendocrine differentiation was expressed as 31.8% in group A, 44% in group B and 70.5% in group C ($p<0.001$, Chi-squared test). Group C included 20 **androgen-independent** cases in which 3 cases were grade 0, 2 were grade 1, 6 were grade 2 and 9 were grade 3. Conversely, for androgen-dependent cases, there were 16, 16, 11 and 5 cases, respectively. Neuroendocrine cells, whether positive or not, alone was not significantly different ($p=0.124$, Chi-squared test); however, the percentage area of positive NE cell expression was significantly different between the **androgen-independent** and -dependent tumors ($p=0.0044$, Chi-squared test). Hormonal therapy may play an important role in the up-regulation of NE differentiation. As well as NE cell expression, whether positive or not, the degree of expression should also be observed to evaluate a poor prognosis, tumor progression and androgen independence.
CT Check Tags: Human; Male
*Androgens: ME, metabolism
Antineoplastic Agents, Hormonal: TU, therapeutic use
*Cell Differentiation
Chromogranins: ME, metabolism
Immunoenzyme Techniques
Neoplasms, Hormone-Dependent: ME, metabolism
*Neoplasms, Hormone-Dependent: PA, pathology
Neoplasms, Hormone-Dependent: TH, therapy
*Neurosecretory Systems: CY, cytology
Prognosis
Prostatic Neoplasms: ME, metabolism
***Prostatic Neoplasms: PA, pathology**
Prostatic Neoplasms: TH, therapy
CN 0 (Androgens); 0 (Antineoplastic Agents, Hormonal); 0 (Chromogranins); 0 (chromogranin A)

L19 ANSWER 22 OF 78 CANCERLIT on STN
AN 2002085432 CANCERLIT
DN 21431954 PubMed ID: 11547123
TI Her-2/neu expression in prostate cancer: high level of expression associated with exposure to hormone therapy and **androgen independent** disease.
AU Shi Y; Brands F H; Chatterjee S; Feng A C; Groshen S; Schewe J; Lieskovsky G; Cote R J
CS Department of Pathology, University of Southern California Keck School of Medicine and Norris Comprehensive Cancer Center, Los Angeles, California 90003, USA.

SO JOURNAL OF UROLOGY, (2001 Oct) 166 (4) 1514-9.
Journal code: 0376374. ISSN: 0022-5347.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Abridged Index Medicus Journals; Priority Journals
OS MEDLINE 2001498341
EM 200112
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB PURPOSE: HER-2/neu is a proto-oncogene that encodes a transmembrane receptor belonging to the family of epidermal growth factor receptors. Increasing evidences indicates that HER-2/neu may contribute to hormone resistance in prostate cancer. We investigated HER-2/neu expression in primary, androgen dependent and advanced **androgen independent** prostate cancer, and its potential value as a marker of disease progression. MATERIALS AND METHODS: Immunohistochemical testing was performed to investigate HER-2/neu expression in 81 patients with prostate cancer, including 31 with pathological stage C disease treated with radical prostatectomy without preoperative androgen ablation therapy (untreated group), 30 with pathological stage C disease treated before surgery with androgen ablation therapy (treated group) and 20 with advanced **androgen independent** prostate cancer (**androgen independent** group). Tumors were classified based on the percent of tumor cells showing HER-2/neu membrane immunoreactivity as low (50% or less) and high (50% or greater) expression. RESULTS: Of the 31 prostate tumors in the untreated group 9 (29%) showed high HER-2/neu expression versus 15 of 30 (50%) in the treated and 17 of 20 (85%) in the **androgen independent** groups. The difference in HER-2/neu expression was significant in the untreated and **androgen independent** ($p < 0.001$) and in the treated and **androgen independent** ($p = 0.016$) groups. There was a significant association of Gleason score with HER-2/neu expression in the untreated group ($p = 0.038$) but not in the treated group. No association was found of tumor substage with HER-2/neu expression. In the untreated group patients with tumors showing high HER-2/neu expression had a decreased survival rate ($p = 0.044$). CONCLUSIONS: High HER-2/neu expression is highly associated with exposure to hormone therapy and androgen independence. It may contribute to androgen independence in prostate cancer and identify patients with prostate cancer more likely to have disease progression, particularly those not exposed to previous hormone therapy.
CT Check Tags: Human; Male; Support, Non-U.S. Gov't
Aged
*Antineoplastic Agents, Hormonal: TU, therapeutic use
*Diethylstilbestrol: TU, therapeutic use
*Gene Expression Regulation, Neoplastic: GE, genetics
*Genes, erbB-2: GE, genetics
Middle Age
Neoplasm Recurrence, Local: EP, epidemiology
*Orchiectomy
***Prostatic Neoplasms: GE, genetics**
Prostatic Neoplasms: MO, mortality
***Prostatic Neoplasms: TH, therapy**
Survival Rate
RN 56-53-1 (Diethylstilbestrol)
CN 0 (Antineoplastic Agents, Hormonal)

L19 ANSWER 23 OF 78 CANCERLIT on STN

AN 2002073718 CANCERLIT
DN 21397939 PubMed ID: 11507044
TI A conditional replication-competent adenoviral vector, Ad-OC-E1a, to cotarget prostate cancer and bone stroma in an experimental model of **androgen-independent** prostate cancer bone metastasis.
AU Matsubara S; Wada Y; Gardner T A; Egawa M; Park M S; Hsieh C L; Zhau H E; Kao C; Kamidono S; Gillenwater J Y; Chung L W
CS Department of Urology, Molecular Urology and Therapeutics Program, University of Virginia School of Medicine, Charlottesville, Virginia 22908, USA.
NC CA85555 (NCI)
SO CANCER RESEARCH, (2001 Aug 15) 61 (16) 6012-9.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2001471449
EM 200109
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB Prostate cancer has a high propensity to metastasize to bone, which often resists hormone, radiation, and chemotherapies. Because of the reciprocal nature of the prostate cancer and bone stroma interaction, we designed a cotargeting strategy using a conditional replication-competent adenovirus to target the growth of tumor cells and their associated osteoblasts. The recombinant Ad-OC-E1a was constructed using a noncollagenous bone matrix protein osteocalcin (OC) promoter to drive the viral early E1a gene with restricted replication in cells that express OC transcriptional activity. Unlike Ad-PSE-E1a, Ad-OC-E1a was highly efficient in inhibiting the growth of PSA-producing (LNCaP, C4-2, and ARCaP) and nonproducing (PC-3 and DU145) human prostate cancer cell lines. This virus was also found to effectively inhibit the growth of human osteoblasts and human prostate stromal cells in vitro. Athymic mice bearing s.c. androgen receptor-negative and PSA-negative PC-3 xenografts responded to a single intratumoral administration of 2 x 10(9) plaque-forming unit(s) of Ad-OC-E1a. In SCID/bg mice, intraosseous growth of androgen receptor-positive and PSA-producing C4-2 xenografts responded markedly to i.v. administrations of a single dose of Ad-OC-E1a. One hundred percent of the treated mice responded to this systemic Ad-OC-E1a therapy with a decline of serum PSA to an undetectable level, and 80% of the mice with PSA rebound responded to the second dose of systemic Ad-OC-E1a. Forty percent of the mice were found to be cured by systemic Ad-OC-E1a without subsequent PSA rebound or tumor cells found in the skeleton. This cotargeting strategy shows a broader spectrum and appears to be more effective than systemic Ad-PSE-E1a in preclinical models of human prostate cancer skeletal metastasis.
CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*Adenovirus E1A Proteins: GE, genetics
Adenoviruses, Human: GE, genetics
Adenoviruses, Human: PH, physiology
Bone Neoplasms: GE, genetics
*Bone Neoplasms: SC, secondary
*Bone Neoplasms: TH, therapy
Cell Division
*Gene Therapy: MT, methods
Growth Inhibitors: BI, biosynthesis
Growth Inhibitors: GE, genetics

Immunohistochemistry
Mice
Mice, Nude
Mice, SCID
Neoplasms, Hormone-Dependent: PA, pathology
Neoplasms, Hormone-Dependent: TH, therapy
Osteocalcin: BI, biosynthesis
*Osteocalcin: GE, genetics
Osteoclasts: PA, pathology
Promoter Regions (Genetics)
Prostate-Specific Antigen: PH, physiology
Prostatic Neoplasms: GE, genetics
***Prostatic Neoplasms: PA, pathology**
***Prostatic Neoplasms: TH, therapy**
Receptors, Androgen: PH, physiology
Stromal Cells: PA, pathology
Virus Replication
Xenograft Model Antitumor Assays
RN 104982-03-8 (Osteocalcin)
CN 0 (Adenovirus E1A Proteins); 0 (Growth Inhibitors); 0 (Receptors, Androgen); EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 24 OF 78 CANCERLIT on STN
AN 2002070842 CANCERLIT
DN 21381055 PubMed ID: 11488070
TI HER2 protein expression and gene amplification in **androgen-independent** prostate cancer.
AU Reese D M; Small E J; Magrane G; Waldman F M; Chew K; Sudilovsky D
CS Urologic Oncology Program, Division of Hematology-Oncology, Comprehensive Cancer Center, University of California, 2356 Sutter St, 5th Floor, San Francisco, CA 94115, USA.
SO AMERICAN JOURNAL OF CLINICAL PATHOLOGY, (2001 Aug) 116 (2) 234-9. Journal code: 0370470. ISSN: 0002-9173.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Abridged Index Medicus Journals; Priority Journals
OS MEDLINE 2001442751
EM 200108
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB The role of the HER2 receptor remains uncertain in the pathogenesis and progression of human prostate cancer. Previous studies have reported widely divergent rates for HER2 expression in primary prostate tumors, probably owing to significant methodologic differences in the studies. Few data exist about the frequency of HER2 protein overexpression and gene amplification in **androgen-independent** prostate cancer (AIPC), although recent xenograft models suggest HER2 expression may be up-regulated in the transition from androgen-dependent to **androgen-independent** disease. We studied the role of HER2 protein in AIPC by immunohistochemical and fluorescence in situ hybridization (FISH) analyses on AIPC specimens using well-characterized and validated reagents. Fourteen (36%) of 39 specimens expressed HER2; however, only 2 (5%) had moderate (2+) expression, and 2 (5%) had high-level (3+) expression. Two (6%) of 36 specimens had gene amplification by FISH. These data suggest that HER2 protein overexpression and gene amplification are relatively uncommon in AIPC.
CT Check Tags: Human; Male; Support, Non-U.S. Gov't
Adenoma: CH, chemistry

Adenoma: PA, pathology
Adenoma: TH, therapy
Adult
Aged
Aged, 80 and over
Androgen Antagonists: TU, therapeutic use
*Androgens: PD, pharmacology
Antibodies, Monoclonal
Biopsy
Bone Neoplasms: CH, chemistry
Bone Neoplasms: SC, secondary
*Gene Amplification
*Gene Expression
Immunoenzyme Techniques
In Situ Hybridization, Fluorescence
Lymphatic Metastasis
Middle Age
Neoplasm Metastasis
Neoplasm Recurrence, Local
Prostatectomy
***Prostatic Neoplasms: CH, chemistry**
Prostatic Neoplasms: PA, pathology
Prostatic Neoplasms: TH, therapy
*Receptor, erbB-2: AN, analysis
*Receptor, erbB-2: GE, genetics
CN 0 (Androgen Antagonists); 0 (Androgens); 0 (Antibodies, Monoclonal); EC 2.7.11.- (Receptor, erbB-2)

L19 ANSWER 25 OF 78 CANCERLIT on STN
AN 2002065788 CANCERLIT
DN 21336417 PubMed ID: 11442654
TI Novel therapeutic strategy for advanced prostate cancer using antisense oligodeoxynucleotides targeting anti-apoptotic genes upregulated after androgen withdrawal to delay **androgen-independent** progression and enhance chemosensitivity.
AU Miyake H; Hara I; Kamidono S; Gleave M E
CS The Prostate Center, Vancouver General Hospital, Vancouver, Canada.. hideakimiyake@hotmail.com
SO INTERNATIONAL JOURNAL OF UROLOGY, (2001 Jul) 8 (7) 337-49. Ref: 61
Journal code: 9440237. ISSN: 0919-8172.
CY Australia
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2001388936
EM 200110
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB Progression to androgen-independence remains the main obstacle to improving survival for patients with advanced prostate cancer. In this review, findings are summarized that have recently been demonstrated to establish novel therapeutic strategy targeting several genes playing functionally important roles after androgen withdrawal and during **androgen-independent** progression. The authors initially characterized changes in gene expression after androgen withdrawal in the androgen-dependent Shionogi and LNCaP tumor models using cDNA arrays. Based on these results, they focused on genes highly upregulated after

androgen ablation (i.e. bcl-2, bcl-xL, TR.PM-2, IGFBP-5), which have anti-apoptotic or mitogenic activities, and thereby confer a resistance to androgen withdrawal as well as cytotoxic chemotherapy. The authors further demonstrated the efficacy of an antisense oligodeoxynucleotide (ODN) strategy for patients with advanced prostate cancer through the inhibition of target gene expression, resulting in a delay in the progression to androgen-independence by enhancing apoptotic cell death induced by androgen ablation and chemotherapy. The authors also showed the effectiveness of combined antisense ODN therapy and cytotoxic chemotherapy by achieving additive or synergistic effects. These findings provide a basic significance for the design of clinical studies using antisense ODN either alone or in combination with chemotherapeutic agents in patients with advanced prostate cancer.

CT Check Tags: Human; Male
*Androgens: PH, physiology
*Apoptosis: GE, genetics
Drug Resistance, Neoplasm
*Gene Therapy: MT, methods
Oligodeoxyribonucleotides, Antisense: TU, therapeutic use
Orchiectomy
***Prostatic Neoplasms: TH, therapy**

CN 0 (Androgens); 0 (Oligodeoxyribonucleotides, Antisense)

L19 ANSWER 26 OF 78 CANCERLIT on STN
AN 2002061069 CANCERLIT
DN 21303175 PubMed ID: 11410491
TI Radioimmunotherapy with (111)In/(90)Y-2IT-BAD-m170 for metastatic prostate cancer.
AU O'Donnell R T; DeNardo S J; Yuan A; Shen S; Richman C M; Lara P N; Griffith I J; Goldstein D S; Kukis D L; Martinez G S; Mirick G R; DeNardo G L; Meyers F J
CS Department of Internal Medicine, Division of Hematology and Oncology, University of California Davis Medical Center, Sacramento, California 95816,. USA.rtodonnell@ucdavis.edu
NC PO1-CA47829 (NCI)
SO CLINICAL CANCER RESEARCH, (2001 Jun) 7 (6) 1561-8.
Journal code: 9502500. ISSN: 1078-0432.
CY United States
DT (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2001347224
EM 200109
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB PURPOSE: Over 31,000 Americans die of **androgen-independent** metastatic prostate cancer each year. New strategies that do not involve hormonal manipulation but instead recognize the biochemical and molecular characteristics of prostate cancer are needed. Radioimmunotherapy (RIT) uses a tumor-specific monoclonal antibody to deliver systemic, targeted radiation to cancer. The objectives of this Phase I study of (111)In-2IT-BAD-m170 (for imaging) and (90)Y-2IT-BAD-m170 (for therapy) were to determine the toxicity and maximum tolerated dose (MTD), the specificity for targeting metastatic prostate cancer, and the efficacy for palliation of pain. EXPERIMENTAL DESIGN: M170 is a mouse monoclonal antibody that targets adenocarcinomas. Patients with adequate renal and liver function, rising prostate-specific antigen, and

androgen-independent metastatic prostate cancer were eligible. After estimation of dosimetry and pharmacokinetics with (111)In-2IT-BAD-m170, a single dose of (90)Y-2IT-BAD-m170 (0.185, 0.370, 0.555, or 0.740 GBq/m(2)) was administered to cohorts of three patients. Pain was assessed objectively by questionnaires before and for 8 weeks after RIT; weekly prostate-specific antigen levels were obtained for 2 months after RIT. RESULTS: The MTD of (90)Y-2IT-BAD-m170 was 0.740 GBq/m(2) for patients that had up to 10% of the axial skeleton involved with prostate cancer. Toxicity was almost exclusively confined to reversible myelosuppression. Metastatic prostate cancer was targeted by (111)In-2IT-BAD-m170 in all 17 patients. The mean radiation dose delivered to 39 bone and 18 nodal metastases by (90)Y-2IT-BAD-m170 was 10.5 Gy/GBq (range 2.8-25.1). Thirteen of 17 patients reported pain before (90)Y-2IT-BAD-m170; 7 of these 13 had a partial or complete resolution of pain that lasted an average of 4.3 weeks. CONCLUSIONS: This study determined the MTD of (111)In/(90)Y-2IT-BAD-m170 in patients with metastatic prostate cancer. The drugs were well tolerated, targeted metastases, and temporarily palliated pain.

CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
Adenocarcinoma: TH, therapy
Aged
Antibodies, Monoclonal: PK, pharmacokinetics
*Antibodies, Monoclonal: TU, therapeutic use
Cohort Studies
*Combined Modality Therapy
*Indium Radioisotopes: DU, diagnostic use
Indium Radioisotopes: PK, pharmacokinetics
Mice
Middle Age
Neoplasm Metastasis
Pain: DT, drug therapy
Prostate-Specific Antigen: BI, biosynthesis
***Prostatic Neoplasms: TH, therapy**
*Radioimmunotherapy
Radiometry
Time Factors
Treatment Outcome
Yttrium Radioisotopes: PK, pharmacokinetics
*Yttrium Radioisotopes: TU, therapeutic use

CN 0 (Antibodies, Monoclonal); 0 (Indium Radioisotopes); 0 (Yttrium Radioisotopes); 0 (monoclonal antibody 2IT-BAD-Lym-1); EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 27 OF 78 CANCERLIT on STN
AN 2002058389 CANCERLIT
DN 21298747 PubMed ID: 11405130
TI [Gene therapy and immunotherapy in prostatic carcinoma]. Gen- und Immuntherapie beim Prostatakarzinom.
AU Fiedler U; Wirth M P
CS Klinik und Poliklinik fur Urologie, Universitatsklinikum, Technische Universitat Dresden, Fetscherstrasse 74, 01307 Dresden.
SO UROLOGE. AUSGABE A, (2001 May) 40 (3) 207-16. Ref: 27
Journal code: 1304110. ISSN: 0340-2592.
CY Germany: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA German

FS MEDLINE; Priority Journals
OS MEDLINE 2001342305
EM 200108
ED Entered STN: 20020726
Last Updated on STN: 20020726
AB Although local prostate cancer (PC) can be cured in most cases by radical prostatectomy, therapies for metastatic and **androgen-independent** PC are limited and rather unsatisfactory. Gene and immunotherapy based on progress in molecular biology are novel treatment options especially for these PC stages. In the field of passive immunotherapy, chimeric/recombinant antibodies and derivatives thereof show promising results in early clinical trails (phase I/II). Before treatment, a careful selection of patients who could profit from this therapy is important (theranostics). Concerning active immunotherapy, administration of dendritic cells loaded with PC-specific tumor antigens seems to be an interesting therapy option. Promising gene therapeutic approaches include antisense and suicide gene therapy. Antisense therapy studies revealed the advantage that even systemic treatment does not lead to strong toxic side effects if the target gene is not involved in important cell functions. Improvement of the gene therapy vectors and identification of new therapeutic genes for PC are essential prerequisites for successful application in humans. Present developments of alternative approaches show that future treatments will be very patient specific.
CT Check Tags: Human; Male
Clinical Trials
English Abstract
*Gene Therapy
*Immunization, Passive
*Immunotherapy, Active
Neoplasm Staging
Outcome and Process Assessment (Health Care)
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**

L19 ANSWER 28 OF 78 CANCERLIT on STN
AN 2001139047 CANCERLIT
DN 21139047 PubMed ID: 11245419
TI Coexpression of the partial androgen receptor enhances the efficacy of prostate-specific antigen promoter-driven suicide gene therapy for prostate cancer cells at low testosterone concentrations.
AU Suzuki S; Tadakuma T; Asano T; Hayakawa M
CS Department of Urology, National Defence Medical College, Tokorozawa, Saitama, Japan.
SO CANCER RESEARCH, (2001 Feb 15) 61 (4) 1276-9.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2001184169
EM 200103
ED Entered STN: 20010515
Last Updated on STN: 20010515
AB The prostate specific antigen (PSA) promoter/enhancer has been clearly demonstrated to be tissue specific, and has been applied to prostate-specific gene therapy. However, the transcription of the PSA gene is strictly androgen dependent, and its promoter activity is very weak at low concentrations of testosterone, which are generally observed in prostatic cancer patients treated with androgen deprivation. In this

study, we used a partial androgen receptor (ARf) containing amino acids 232-429 and 481-657 to transactivate the PSA gene without androgens. We made two expression vectors, ARfPPLUC and ARfPPTK. They contained ARf cDNA driven by cytomegalovirus promoter and cDNAs of either firefly luciferase (LUC) or herpes simplex virus thymidine kinase (TK) driven by PSA promoter/enhancer (PP). The expressed ARf enhanced the PP activity by about 110-fold in the PSA-producing prostate cancer cell line, LNCaP, under low testosterone concentrations. Moreover, in a PSA-nonproducing prostate cancer cell line, DU145, ARf also enhanced the PP activity by about 60-fold in an **androgen-independent** manner. In a growth inhibition assay, ARfPPTK treated with ganciclovir was found to inhibit the cell growth of LNCaP cells much more effectively than PPTK. Furthermore, in contrast to PPTK, ARfPPTK also had an inhibitory effect on DU145 cells. This system is thus considered to provide a useful therapeutic option in patients with prostate cancer who are receiving hormonal therapy.

CT Check Tags: Human; Male
Cell Division: GE, genetics
Cloning, Molecular
DNA, Complementary: GE, genetics
Ganciclovir: AD, administration & dosage
*Gene Therapy: MT, methods
Genetic Vectors: GE, genetics
Peptide Fragments: BI, biosynthesis
Peptide Fragments: GE, genetics
Peptide Fragments: PH, physiology
Plasmids: GE, genetics
*Promoter Regions (Genetics)
*Prostate-Specific Antigen: GE, genetics
Prostatic Neoplasms: GE, genetics
Prostatic Neoplasms: ME, metabolism
***Prostatic Neoplasms: TH, therapy**
Receptors, Androgen: BI, biosynthesis
Receptors, Androgen: GE, genetics
*Receptors, Androgen: PH, physiology
*Testosterone: ME, metabolism
Thymidine Kinase: GE, genetics
Thymidine Kinase: ME, metabolism
Trans-Activation (Genetics)
Transfection
Tumor Cells, Cultured

RN 57-85-2 (Testosterone); 82410-32-0 (Ganciclovir)

CN 0 (DNA, Complementary); 0 (Genetic Vectors); 0 (Peptide Fragments); 0 (Plasmids); 0 (Receptors, Androgen); EC 2.7.1.21 (Thymidine Kinase); EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 29 OF 78 CANCERLIT on STN

AN 2001107430 CANCERLIT

DN 21107430 PubMed ID: 11170149

TI A monoclonal antibody cytolytic to **androgen independent** DU145 and PC3 human prostatic carcinoma cells.

AU Talwar G P; Gupta R; Gupta S K; Malhotra R; Khanna R; Mitra D K; Sehgal S; Minz R; Kumar A

CS Talwar Research Foundation, E-6, Neb Valley, Neb Serai, New Delhi, 110 068, India.. talwar37@hotmail.com

SO PROSTATE, (2001 Feb 15) 46 (3) 207-13.
Journal code: 8101368. ISSN: 0270-4137.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2001150037
EM 200103
ED Entered STN: 20010515
Last Updated on STN: 20010515
AB BACKGROUND: While a range of therapeutic products is available for androgen-dependent prostatic cancer, no specific intervention modality exists for **androgen-independent** prostatic cancer. The objective of this research was to explore whether epitopes exist on **androgen-independent** prostatic DU145 cancer cells, which could be susceptible to cytotoxic action of specific antibodies. METHODS: Hybrid cell clones were developed by immunization of mice with DU145 cells and tested for immunoreactivity by solid phase EIA and cytotoxicity in vitro on DU145 in the presence of the complement, employing colorimetric quantitation by MTS (3- (4-, 5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-(4-sulfophenyl)-2H-tetrazolium). Binding and cytotoxicity studies were also carried out by flow-cytometry. RESULTS: Of 15 stabilized clones immunoreactive with DU145 cells, one monoclonal antibody (mAb 730) manifested cytotoxicity on DU145 cells. Approximately 80% of cells in the DU145 cell line were susceptible to lysis with this antibody at saturating levels. This figure corresponded quantitatively to the number of cells binding with this antibody as determined by Flow-cytometry. Staining with ethidium monoazide bromide (EMA) showed that the cell binding the antibody was also the one killed by the antibody in the presence of the complement. MAb 730 was also cytotoxic to PC3, another **androgen-independent** human prostatic cancer cell line. This antibody is devoid of classical autoantibody reactivities and does not react with normal human liver, thyroid, kidney, pancreas, and adrenal tissues, as determined by immunofluorescence. Also, it shows negative immuno-reactivity to benign glandular tissue but is observed to positively react with neoplastic prostate tissue. CONCLUSIONS: Epitopes exist on **androgen-independent** prostatic cancer cells that are susceptible to cytolysis by monoclonal antibodies and these could be investigated for potential immunotherapy.

CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't
Antibodies, Monoclonal: IM, immunology
*Antibodies, Monoclonal: TO, toxicity
Antibody-Dependent Cell Cytotoxicity: IM, immunology
*Carcinoma: IM, immunology
*Carcinoma: TH, therapy
Cell Fusion
Complement: IM, immunology
Dose-Response Relationship, Immunologic
Hybrid Cells: IM, immunology
Hybrid Cells: SE, secretion
Immunoenzyme Techniques
Immunohistochemistry
Mice
Neoplasms, Hormone-Dependent: IM, immunology
Neoplasms, Hormone-Dependent: TH, therapy
Prostate-Specific Antigen: IM, immunology
***Prostatic Neoplasms: IM, immunology**
***Prostatic Neoplasms: TH, therapy**
Spleen: CY, cytology
Spleen: IM, immunology
Tooth, Supernumerary
Tumor Cells, Cultured

RN 9007-36-7 (Complement)
CN 0 (Antibodies, Monoclonal); EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 30 OF 78 CANCERLIT on STN
AN 2000468839 CANCERLIT
DN 20468839 PubMed ID: 11016624
TI The dual impact of coxsackie and adenovirus receptor expression on human prostate cancer gene therapy.
AU Okegawa T; Li Y; Pong R C; Bergelson J M; Zhou J; Hsieh J T
CS Department of Urology, The University of Texas Southwestern Medical Center, Dallas 75390-9110, USA.
NC AI35667 (NIAID)
CA 73017 (NCI)
HL 54734 (NHLBI)
SO CANCER RESEARCH, (2000 Sep 15) 60 (18) 5031-6.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2000463794
EM 200010
ED Entered STN: 20001128
Last Updated on STN: 20001128
AB In a recent paper, we reported a significant difference in coxsackie and adenovirus receptor (CAR) from several human bladder cancer cell lines that correlated with their sensitivities to adenoviral infection (Y. Li, R-C. Pong, J. M. Bergelson, M. C. Hall, A. I. Sagalowsky, C-P. Tseng, Z. Wang, and J. T. Hsieh, Cancer Res., 59: 325-330, 1999). In human prostate cancer, CAR protein is down-regulated in the highly tumorigenic PC3 cell line, which suggests that, in addition to its function as a viral receptor, CAR may have a pathophysiological role in prostate cancer progression. In this paper, we document that CAR does not merely enhance the viral sensitivity of prostate cancer cells but also acts as a tumor inhibitor for **androgen-independent** prostate cancer cells. Our data indicate that CAR is a potential therapeutic agent for increasing the efficacy of prostate cancer therapy.
CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Adenoviridae: GE, genetics
Cell Division: PH, physiology
*Gene Therapy
Genetic Vectors
Mice
Mice, Nude
Neoplasm Transplantation
Prostatic Neoplasms: ME, metabolism
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**
Receptors, Virus: BI, biosynthesis
Receptors, Virus: GE, genetics
*Receptors, Virus: PH, physiology
Transfection
Tumor Cells, Cultured
CN 0 (CAR receptor); 0 (Genetic Vectors); 0 (Receptors, Virus)

L19 ANSWER 31 OF 78 CANCERLIT on STN
AN 2000458223 CANCERLIT
DN 20458223 PubMed ID: 11005213

TI FISH analysis of gene aberrations (MYC, CCND1, ERBB2, RB, and AR) in advanced prostatic carcinomas before and after androgen deprivation therapy.

AU Kaltz-Wittmer C; Klenk U; Glaessgen A; Aust D E; Diebold J; Lohrs U; Baretton G B

CS Institute of Pathology, Ludwig-Maximilians University, Munich, Germany.

SO LABORATORY INVESTIGATION, (2000 Sep) 80 (9) 1455-64.
Journal code: 0376617. ISSN: 0023-6837.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS MEDLINE; Priority Journals

OS MEDLINE 2000450229

EM 200010

ED Entered STN: 20001128
Last Updated on STN: 20001128

AB Genetic mechanisms leading to **androgen-independent** growth in advanced prostatic carcinomas (PC) are still poorly understood. Analysis of genes potentially involved in the regulation of tumor cell proliferation and apoptosis might confer better insight into this process and might lead to improved therapeutic strategies. Fluorescence in situ hybridization (FISH) analysis of dissociated nuclei with DNA probes for MYC (8q24)/#8, cyclin D1 gene (CCND1; 11q13)/#11, ERBB2 (17q13)/#17, the androgen receptor gene (AR; Xq12)/#X, and the retinoblastoma gene (RB; 13q14) was applied to formalin-fixed tissue from 63 patients with advanced PC after androgen deprivation therapy (ADT); matched tumor tissue before ADT was also available in 22 of these cases. The cut-points used were: "increased copy number," > or = 30% of all nuclei with increased FISH signals (centromere and/or gene); "amplification," > or = 15% of nuclei with "increased gene copy number." CCND1 and MYC gene "amplifications" were present before ADT in 25% and 33% of the cases, respectively; the frequency of these "amplifications" increased to 37% and 57% after ADT. Loss of the RB gene was nearly four times more frequent after ADT than before therapy (22% versus 6%). AR and ERBB2 gene "amplifications" occurred only after ADT in 36% and 30% of cases, respectively. With the exception of the AR gene, the copy number increase was low. After treatment, MYC and AR gene "amplifications" correlated with the proliferation rate (Ki-67/MIB1 index; p = 0.01 and p = 0.04), whereas ERBB2 "amplifications" were associated with increased apoptotic index (PCD/TUNEL; p = 0.016). However, no correlation between FISH results and clinical follow-up could be established. FISH analysis of genes putatively involved in PC progression revealed characteristic patterns of aberrations in advanced PC before and after ADT. Distinct changes in gene copy number before and after therapy suggests possible involvement of these genes in the escape from androgen control.

CT Check Tags: Human; Male; Support, Non-U.S. Gov't
Aged
*Androgen Antagonists: TU, therapeutic use
Cyclin D1: GE, genetics
Gene Dosage
Genes, Retinoblastoma
Genes, erbB-2
Genes, myc
*In Situ Hybridization, Fluorescence
Ki-67 Antigen: AN, analysis
Middle Age
***Prostatic Neoplasms: GE, genetics**
Prostatic Neoplasms: TH, therapy
Receptors, Androgen: GE, genetics

RN 136601-57-5 (Cyclin D1)
CN 0 (Androgen Antagonists); 0 (Ki-67 Antigen); 0 (Receptors, Androgen)

L19 ANSWER 32 OF 78 CANCERLIT on STN
AN 2000383423 CANCERLIT
DN 20383423 PubMed ID: 10928288
TI Apoptosis in prostate carcinogenesis. A growth regulator and a therapeutic target.
AU Bruckheimer E M; Kyprianou N
CS Department of Molecular Biology and Cancer Center, University of Maryland School of Medicine, Baltimore 21201, USA.
NC R01 DK 53525-01 (NIDDK)
SO CELL AND TISSUE RESEARCH, (2000 Jul) 301 (1) 153-62. Ref: 120
Journal code: 0417625. ISSN: 0302-766X.
CY GERMANY: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2001040685
EM 200012
ED Entered STN: 20010423
Last Updated on STN: 20010423
AB Development of effective therapeutic modalities for the treatment of human cancer relies heavily upon understanding the molecular alterations that result in initiation and progression of the tumorigenic process. Many of the molecular changes identified in human prostate tumorigenesis so far play key roles in apoptosis regulation. Apoptosis represents a universal and exquisitely efficient cellular suicide pathway. Since the therapeutic goal is to trigger tumor-selective apoptotic cell death (without clinically significant effects on the host), elucidation of the mechanisms underlying apoptosis deregulation will lead to the identification of specific cellular components for targeting therapeutic interventions. As our understanding of its vital role in the development and growth of the prostate gland has expanded, numerous genes that encode apoptotic regulators have been identified that are severely impaired in prostate cancer cells. In addition, the expression of apoptotic modulators within prostatic tumors appears to correlate with tumor sensitivity to traditional therapies such as hormonal ablation and radiotherapy. No strict correlation between apoptosis induction and a patient's long-term prognosis has emerged, perhaps due to the fact that the ability to achieve initial remission alone does not adequately predict long-term outcome. This review will encompass the known molecular changes intimately involved in the apoptotic pathway which have potential prognostic value in disease progression, as well as therapeutic significance in the enhancement of the apoptotic response to novel and established treatment strategies for the treatment of androgen-dependent and **androgen-independent** prostatic tumors. The main focus will be on the role of the transforming growth factor-beta (TGF-beta) signaling pathway, bcl-2 and the bcl-2 family members, the caspase cascade (apoptosis executioners), and the Fas pathway in induction and regulation of apoptosis following therapeutic stimuli for the management of advanced prostate cancer.
CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Antigens, CD95: PH, physiology
*Apoptosis: PH, physiology
Caspases: ME, metabolism
Caspases: PH, physiology

Cell Cycle
Mice
Prostatic Neoplasms: ME, metabolism
***Prostatic Neoplasms: PP, physiopathology**
***Prostatic Neoplasms: TH, therapy**
Proto-Oncogene Proteins c-bcl-2: PH, physiology
Transforming Growth Factor beta: PH, physiology
CN 0 (Antigens, CD95); 0 (Proto-Oncogene Proteins c-bcl-2); 0 (Transforming Growth Factor beta); 0 (transforming growth factor beta1); EC 3.4.22.- (Caspases)

L19 ANSWER 33 OF 78 CANCERLIT on STN
AN 2000371870 CANCERLIT
DN 20371870 PubMed ID: 10917202
TI Inhibition of LncaP prostate cancer cells by means of androgen receptor antisense oligonucleotides.
AU Eder I E; Culig Z; Ramoner R; Thurnher M; Putz T; Nessler-Menardi C; Tiefenthaler M; Bartsch G; Klocker H
CS Department of Urology, University of Innsbruck, Austria.
SO CANCER GENE THERAPY, (2000 Jul) 7 (7) 997-1007.
Journal code: 9432230. ISSN: 0929-1903.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2001017552
EM 200011
ED Entered STN: 20010423
Last Updated on STN: 20010423
AB Currently available methods for treatment of human prostatic carcinoma aim to inactivate the androgen receptor (AR) by androgen deprivation or blockade with anti-androgens. Failure of endocrine therapy and tumor progression is characterized by **androgen-independent** growth despite high levels of AR expression in metastatic disease. We inhibited AR expression in LNCaP prostate tumor cells by using antisense AR oligodeoxynucleotides (ODNs) and explored whether antisense AR treatment would be conceivable as a therapy for advanced prostate cancer. Among the various AR antisense ODNs tested, a 15-base ODN targeting the CAG repeats encoding the poly-glutamine region of the AR (as750/15) was found to be most effective. Treatment of LNCaP cells with as750/15 reduced AR expression to approximately 2% within 24 hours compared with mock-treated controls. AR down-regulation resulted in significant cell growth inhibition, strongly reduced secretion of the androgen-regulated prostate-specific antigen, reduction of epidermal growth factor receptor expression, and an increase in apoptotic cells. Mis-sense and mismatched control ODNs had no or only slight effects. Antisense inhibition was also very efficient in LNCaP-abl cells, a subline established after long-term androgen ablation of LNCaP cells, resulting in inhibition of AR expression and cell proliferation that was similar to that seen for parental LNCaP cells. This study shows that inhibition of AR expression by antisense AR ODNs may be a promising new approach for treatment of advanced human prostate cancer.
CT Check Tags: Human; Male; Support, Non-U.S. Gov't
Apoptosis
Cell Division
DNA Primers: CH, chemistry
Down-Regulation
Enzyme-Linked Immunosorbent Assay
Gene Therapy

Immunoblotting
*Oligodeoxyribonucleotides, Antisense: TU, therapeutic use
Prostate-Specific Antigen: AN, analysis
Prostatic Neoplasms: ME, metabolism
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**
RNA, Messenger: AN, analysis
Receptor, Epidermal Growth Factor: ME, metabolism
*Receptors, Androgen: GE, genetics
Receptors, Androgen: ME, metabolism
Reverse Transcriptase Polymerase Chain Reaction
Time Factors
Tumor Cells, Cultured
CN 0 (DNA Primers); 0 (Oligodeoxyribonucleotides, Antisense); 0 (RNA, Messenger); 0 (Receptors, Androgen); EC 2.7.11.- (Receptor, Epidermal Growth Factor); EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 34 OF 78 CANCERLIT on STN
AN 2000354708 CANCERLIT
DN 20354708 PubMed ID: 10898343
TI Establishment of human prostate carcinoma skeletal metastasis models.
AU Zhau H E; Li C L; Chung L W
CS Department of Urology, University of Virginia Health System, Charlottesville 22908, USA.
NC CA6334 (NCI)
CA76620 (NCI)
SO CANCER, (2000 Jun 15) 88 (12 Suppl) 2995-3001. Ref: 42
Journal code: 0374236. ISSN: 0008-543X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Abridged Index Medicus Journals; Priority Journals
OS MEDLINE 2000354708
EM 200007
ED Entered STN: 20000811
Last Updated on STN: 20000811
AB BACKGROUND: Prostate carcinoma progression from an androgen dependent (AD) state to an **androgen independent** (AI) state occurs clinically in patients who undergo hormonal therapy. In their laboratory, the authors developed two human prostate carcinoma skeletal metastasis models, the LNCaP progression model and the ARCaP model, to investigate phenotypic and genotypic changes of prostate carcinoma cells during disease progression and to understand molecular pathways for potential therapeutic targeting. METHODS: LNCaP or ARCaP cells were inoculated in athymic mice and were exposed to selective hormonal conditions both in vivo and in vitro. The effects of various hormonal treatment regimens on tumor volumes and distant metastasis and the effects of bone stromal cells on prostate specific antigen (PSA) expression by prostate carcinoma cells were evaluated. RESULTS: The authors propose that prostate carcinoma progression from the AD state to the AI state assumes three AI phenotypes: AI that remains androgen responsive, AI that is unresponsive to androgen stimulation, and AI that is suppressed by or hypersensitive to androgen. AI prostate carcinoma cells interacted reciprocally with osteoblasts to produce enhanced tumor growth and osteoblastic reaction when they are deposited in bone. Bone stromal cell conditioned media stimulated prostate carcinoma cell growth and suppressed its PSA expression, as also evidenced by androgen receptor-mediated transactivation of PSA promoter reporter

activity. Conditioned media obtained from prostate carcinoma cells also stimulated osteoblastic cell growth in vitro. A novel gene therapy strategy is being developed to target prostatic tumor epithelium and its supporting stroma using tissue specific and tumor-restricted, promoter-directed toxic gene expression in both cellular compartments. In addition, new strategies are being designed to target the tumor endothelial system in the stroma and tumor cell-extracellular matrix interaction mediated by isotype specific integrins. CONCLUSIONS: Prostate carcinoma skeletal metastasis models may prove useful in developing a new targeting strategy for the prevention and treatment of patients with prostate carcinoma.

CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, Non-P.H.S.; Support, U.S. Gov't, P.H.S.
*Bone Neoplasms: SC, secondary
*Disease Models, Animal
Mice
***Prostatic Neoplasms: PA, pathology**
Prostatic Neoplasms: TH, therapy

L19 ANSWER 35 OF 78 CANCERLIT on STN
AN 2000297895 CANCERLIT
DN 20297895 PubMed ID: 10841200
TI An update on prostate cancer research.
AU Small E J; Reese D M
CS University of California, San Francisco, Comprehensive Cancer Center, 94115, USA.. smalle@medicine.ucsf.edu
SO CURRENT OPINION IN ONCOLOGY, (2000 May) 12 (3) 265-72. Ref: 67
Journal code: 9007265. ISSN: 1040-8746.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2000424716
EM 200009
ED Entered STN: 20001012
Last Updated on STN: 20001012
AB The pathogenesis of prostate cancer reflects complex interactions among environmental and genetic factors. Recent advances suggest molecular mechanisms that may explain geographic and ethnic variations in prostate cancer incidence, and understanding of molecular disease progression is advancing rapidly. Clinically, the case for screening has become stronger, and declining prostate cancer mortality rates may be due in part to early detection and treatment. Improved risk assessment for patients with localized disease is now available, although further refinement in predictive algorithms will need to incorporate validated molecular prognostic markers. Treatment options for patients with localized prostate cancer have expanded and the role of androgen deprivation further delineated. Finally, treatment strategies for patients with **androgen-independent** disease have also expanded, although novel therapies are required to improve survival in this group of patients.
CT Check Tags: Human; Male
Clinical Trials
***Prostatic Neoplasms**
Prostatic Neoplasms: DI, diagnosis
Prostatic Neoplasms: EP, epidemiology
Prostatic Neoplasms: PA, pathology

Prostatic Neoplasms: TH, therapy
Risk Assessment

L19 ANSWER 36 OF 78 CANCERLIT on STN
AN 2000273330 CANCERLIT
DN 20273330 PubMed ID: 10815883
TI Antisense TRPM-2 oligodeoxynucleotides chemosensitize human **androgen-independent** PC-3 prostate cancer cells both in vitro and in vivo.
AU Miyake H; Chi K N; Gleave M E
CS The Prostate Centre, Vancouver General Hospital, British Columbia, Canada.
SO CLINICAL CANCER RESEARCH, (2000 May) 6 (5) 1655-63.
Journal code: 9502500. ISSN: 1078-0432.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2000410710
EM 200008
ED Entered STN: 20001012
Last Updated on STN: 20001012
AB Although numerous chemotherapeutic regimens have been evaluated for patients with hormone-refractory prostate cancer, none has improved survival. Testosterone-repressed prostate message-2 (TRPM-2), which is highly up-regulated after androgen withdrawal and during **androgen -independent** progression in prostate cancer, has been shown to inhibit apoptosis induced by various kinds of stimuli. The objectives in this study were to test whether antisense (AS) oligodeoxynucleotides (ODNs) targeted against TRPM-2 enhance chemosensitivity in human **androgen-independent** prostate cancer PC-3 cells both in vitro and in vivo. Initially, the potency of 10 AS ODNs targeting various regions of the TRPM-2 mRNA were evaluated, and the AS ODN targeted to the TRPM-2 translation initiation site (AS ODN#2) was found to be the most potent sequence for inhibiting TRPM-2 expression in PC-3 cells. Despite significant dose-dependent and sequence-specific suppression of TRPM-2 expression, AS ODN#2 had no effect on growth of PC-3 cells both in vitro and in vivo. However, pretreatment of PC-3 cells with AS ODN#2 significantly enhanced chemosensitivity of Taxol (paclitaxel) and mitoxantrone in vitro. Characteristic apoptotic DNA laddering and cleavage of poly(ADP-ribose) polymerase were observed after combined treatment with AS ODN#2 plus paclitaxel or mitoxantrone but not with either agent alone. In vivo administration of AS ODN#2 plus either paclitaxel or mitoxantrone significantly decreased PC-3 tumor volume by 80 or 60%, respectively, compared with mismatch control ODN plus either paclitaxel or mitoxantrone. In addition, terminal deoxynucleotidyl transferase-mediated nick end labeling staining revealed increased apoptotic cells in tumors treated with AS ODN#2 plus paclitaxel or mitoxantrone. These findings confirm that TRPM-2 overexpression confers resistance to cytotoxic chemotherapy in prostate cancer cells and illustrates the potential utility of combined treatment with AS TRPM-2 ODN plus chemotherapeutic agents for patients with hormone-refractory prostate cancer.
CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't
Androgens: PH, physiology
Antineoplastic Agents: PD, pharmacology
Cell Division: DE, drug effects
Cell Survival: DE, drug effects
DNA Fragmentation: DE, drug effects
Dose-Response Relationship, Drug
Drug Synergism

Gene Expression Regulation, Neoplastic: DE, drug effects
*Glycoproteins: GE, genetics
In Situ Nick-End Labeling
Mice
Mice, Inbred BALB C
Mice, Nude
Mitoxantrone: PD, pharmacology
Oligodeoxyribonucleotides, Antisense: IP, isolation & purification
*Oligodeoxyribonucleotides, Antisense: PD, pharmacology
Oligodeoxyribonucleotides, Antisense: TU, therapeutic use
Paclitaxel: PD, pharmacology
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**
RNA, Messenger: DE, drug effects
RNA, Messenger: GE, genetics
RNA, Messenger: ME, metabolism
Thionucleotides: IP, isolation & purification
Thionucleotides: PD, pharmacology
Thionucleotides: TU, therapeutic use
Tumor Cells, Cultured
RN 33069-62-4 (Paclitaxel); 65271-80-9 (Mitoxantrone)
CN 0 (Androgens); 0 (Antineoplastic Agents); 0 (Glycoproteins); 0 (Oligodeoxyribonucleotides, Antisense); 0 (RNA, Messenger); 0 (Thionucleotides); 0 (clusterin)

L19 ANSWER 37 OF 78 CANCERLIT on STN
AN 2000223938 CANCERLIT
DN 20223938 PubMed ID: 10759680
TI Adenovirus-mediated suicide-gene therapy using the herpes simplex virus thymidine kinase gene in cell and animal models of human prostate cancer: changes in tumour cell proliferative activity.
AU Cheon J; Kim H K; Moon D G; Yoon D K; Cho J H; Koh S K
CS Department of Urology and Pathology, Korea University Hospital, Seoul, Korea.. jcheon@ns.kumc.or.kr
SO BJU INTERNATIONAL, (2000 Apr) 85 (6) 759-66.
Journal code: 100886721. ISSN: 1464-4096.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2000223938
EM 200005
ED Entered STN: 20000622
Last Updated on STN: 20000622
AB OBJECTIVES: To determine the feasibility and efficacy of suicide-gene therapy using adenovirus (Ad)-mediated herpes simplex virus thymidine kinase (HSV-TK) and the prodrug acyclovir, and to evaluate changes in the biological phenotype for tumour cell proliferative activity after suicide-gene therapy in animal models of human prostate cancer. MATERIALS AND METHODS: Using a replication-defective adenoviral vector (cytomegalovirus, CMV) containing the beta-galactosidase gene (Ad-CMV-beta-gal) as a control and Ad-CMV-TK as the therapeutic vector under the transcriptional control of the CMV promoter, transduction efficiency was assessed in vitro by infecting LNCaP and PC-3 androgen-dependent and independent human prostate cancer cells with Ad-CMV-beta-gal, and using X-gal staining. The TK activity in prostate cancer cells infected with Ad-CMV-TK was determined by measuring TK-mediated [3H]-gancyclovir phosphorylation. The sensitivity of LNCaP and PC-3 cells to Ad-CMV-TK in vitro was determined after infection with the

therapeutic vector with or without acyclovir. The inhibition of PC-3 tumour growth in vivo induced by the Ad-CMV-TK/acyclovir suicide-gene system was assessed in separate and controlled experiments using human prostate cancer mouse models. Ki-67 proliferative antigen and proliferating cell nuclear antigen (PCNA), both useful proliferative indices, were evaluated using immunohistochemical staining (MIB-1 monoclonal antibody and monoclonal anti-PCNA antibody) in formalin-fixed, paraffin-embedded tissues from gene therapy-treated and control animals. RESULTS: The mean TK activity was significantly higher in LNCaP and PC-3 cells infected with Ad-CMV-TK than in cells infected with Ad-CMV-beta-gal, used as a control ($P < 0.05$). The growth of human prostate cancer cells with Ad-CMV-TK was significantly inhibited by adding acyclovir in vitro ($P < 0.05$). In the in vivo experiments using the PC-3 human prostate cancer mouse model, tumour volume and growth was lower in mice treated with Ad-CMV-TK/acyclovir than in those treated with Ad-CMV-TK only, acyclovir only or untreated (controls) ($P < 0.05$). Histochemical staining of tumour tissues showed that Ad-CMV-TK/acyclovir destroyed PC-3 tumours through tumour cell death and apoptosis, with local lymphatic infiltration. The mean PCNA labelling index in prostate cancer cells of mice treated with Ad-CMV-TK/acyclovir was significantly lower than that in untreated controls ($P < 0.05$, Mann-Whitney U-test). The Ki-67 labelling index in prostate cancer cells of mice treated with Ad-CMV-TK/acyclovir was also lower than that in untreated controls ($P < 0.05$, Student's t-test). Adenovirus-mediated suicide-gene therapy using the HSV-TK gene decreased the proliferative activity of PC-3 human prostatic cancer cells in vivo. CONCLUSIONS: Adenovirus-mediated suicide-gene therapy using an HSV-TK/acyclovir system provided effective therapy in an experimental human prostate cancer mouse model, by significantly inhibiting tumour growth and decreasing the proliferative activity of human prostate cancer cells. Such therapy could be developed as a novel method for treating patients with **androgen-independent** prostate cancer.

CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't
Antiviral Agents: TU, therapeutic use
Cytomegalovirus: EN, enzymology
*Cytomegalovirus: GE, genetics
Ganciclovir: TU, therapeutic use
Gene Expression
*Gene Therapy: MT, methods
Genetic Vectors: AD, administration & dosage
Mice
***Prostatic Neoplasms: TH, therapy**
*Simplexvirus: EN, enzymology
Statistics, Nonparametric
*Thymidine Kinase: GE, genetics
Tumor Cells, Cultured
beta-Galactosidase: GE, genetics

RN 82410-32-0 (Ganciclovir)

CN 0 (Antiviral Agents); 0 (Genetic Vectors); EC 2.7.1.21 (Thymidine Kinase); EC 3.2.1.23 (beta-Galactosidase)

L19 ANSWER 38 OF 78 CANCERLIT on STN

AN 2000034901 CANCERLIT

DN 20034901 PubMed ID: 10569613

TI The utility of tissue transglutaminase as a marker of apoptosis during treatment and progression of prostate cancer.

AU Rittmaster R S; Thomas L N; Wright A S; Murray S K; Carlson K; Douglas R C; Yung J; Messieh M; Bell D; Lazier C B

CS Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada.

SO JOURNAL OF UROLOGY, (1999 Dec) 162 (6) 2165-9.
Journal code: 0376374. ISSN: 0022-5347.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Abridged Index Medicus Journals; Priority Journals
OS MEDLINE 2000034901
EM 200001
ED Entered STN: 20000221
Last Updated on STN: 20000221

AB PURPOSE: To determine the extent of cell proliferation and apoptosis during treatment and progression of prostate cancer and to determine whether staining for tissue transglutaminase is a better histological marker than TUNEL for neoadjuvant androgen ablation treatment of localized prostate cancer. MATERIALS AND METHODS: Immunocytochemistry techniques were used on archival prostate tissue from four groups of men: 14 men with BPH, 18 men with untreated, localized prostate cancer, 21 men with localized prostate cancer who received neoadjuvant hormone therapy prior to prostatectomy and 18 men with metastatic **androgen-independent** prostate cancer. Cell proliferation was evaluated by staining for the Ki67 nuclear antigen, and apoptosis was evaluated by staining for DNA fragmentation (TUNEL technique) and tissue transglutaminase (tTG). Image analysis was used to quantitate the results. RESULTS: TUNEL staining increased by 37% in localized prostate cancer compared with BPH, with a further increase of 43% seen after neoadjuvant therapy, although variation was such that neither was statistically significant. In **androgen-independent** cancer, TUNEL staining was decreased compared with neoadjuvant hormone treated cancer ($p = 0.02$). Staining for tTG was not increased in untreated prostate cancer compared with BPH; however, staining more than doubled after neoadjuvant therapy, compared with untreated prostate cancer ($p = 0.04$). Staining for tTG was markedly decreased in **androgen-independent** cancer ($p = 0.07$ compared with BPH and $p = 0.0004$ compared with neoadjuvant hormone treated cancer). Ki67 immunoreactivity did not significantly change in localized prostate cancer, either before or after neoadjuvant therapy, compared with BPH, but it more than doubled in **androgen-independent** prostate cancer ($p = 0.07$ compared with BPH and $p = 0.05$ compared with untreated prostate cancer). CONCLUSIONS: This study shows that cell proliferation increases and apoptosis decreases as prostate cancer progresses to androgen independence, and, that of the markers used in this study, tissue transglutaminase most accurately reflects the anticipated effect of neoadjuvant hormone therapy on localized prostate cancer. An assessment of these parameters provides a valuable tool for appraising new prostate cancer therapies.

CT Check Tags: Human; Male; Support, Non-U.S. Gov't

*Apoptosis
Cell Division
DNA Fragmentation
Disease Progression
*GTP-Binding Proteins: AN, analysis
Immunohistochemistry
Neoplasm Metastasis
Prostatic Hyperplasia: EN, enzymology
Prostatic Hyperplasia: GE, genetics
Prostatic Hyperplasia: PA, pathology
Prostatic Neoplasms: CH, chemistry
***Prostatic Neoplasms: EN, enzymology**
Prostatic Neoplasms: GE, genetics

***Prostatic Neoplasms: PA, pathology**
Prostatic Neoplasms: TH, therapy
*Transglutaminases: AN, analysis
*Tumor Markers, Biological: AN, analysis
CN 0 (Tumor Markers, Biological); EC 2.3.2.- (transglutaminase 2); EC 2.3.2.13 (Transglutaminases); EC 3.6.1.- (GTP-Binding Proteins)

L19 ANSWER 39 OF 78 CANCERLIT on STN
AN 2000018260 CANCERLIT
DN 20018260 PubMed ID: 10550143
TI Eligibility and response guidelines for phase II clinical trials in **androgen-independent** prostate cancer: recommendations from the Prostate-Specific Antigen Working Group.
CM Erratum in: J Clin Oncol 2000 Jul;18(13):2644
AU Bubley G J; Carducci M; Dahut W; Dawson N; Daliani D; Eisenberger M; Figg W D; Freidlin B; Halabi S; Hudes G; Hussain M; Kaplan R; Myers C; Oh W; Petrylak D P; Reed E; Roth B; Sartor O; Scher H; Simons J; Sinibaldi V; Small E J; Smith M R; Trump D L; Wilding G; +
CS Beth Israel Deaconess Medical Center, Dana Farber Cancer Center, and Massachusetts General Hospital, Boston, MA, USA.
SO JOURNAL OF CLINICAL ONCOLOGY, (1999 Nov) 17 (11) 3461-7.
Journal code: 8309333. ISSN: 0732-183X.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 2000018260
EM 200001
ED Entered STN: 20000616
Last Updated on STN: 20000616
AB PURPOSE: Prostate-specific antigen (PSA) is a glycoprotein that is found almost exclusively in normal and neoplastic prostate cells. For patients with metastatic disease, changes in PSA will often antedate changes in bone scan. Furthermore, many but not all investigators have observed an association between a decline in PSA levels of 50% or greater and survival. Since the majority of phase II clinical trials for patients with **androgen-independent** prostate cancer (AIPC) have used PSA as a marker, we believed it was important for investigators to agree on definitions and values for a minimum set of parameters for eligibility and PSA declines and to develop a common approach to outcome analysis and reporting. We held a consensus conference with 26 leading investigators in the field of AIPC to define these parameters. RESULT: We defined four patient groups: (1) progressive measurable disease, (2) progressive bone metastasis, (3) stable metastases and a rising PSA, and (4) rising PSA and no other evidence of metastatic disease. The purpose of determining the number of patients whose PSA level drops in a phase II trial of AIPC is to guide the selection of agents for further testing and phase III trials. We propose that investigators report at a minimum a PSA decline of at least 50% and this must be confirmed by a second PSA value 4 or more weeks later. Patients may not demonstrate clinical or radiographic evidence of disease progression during this time period. Some investigators may want to report additional measures of PSA changes (ie, 75% decline, 90% decline). Response duration and the time to PSA progression may also be important clinical end point. CONCLUSION: Through this consensus conference, we believe we have developed practical guidelines for using PSA as a measurement of outcome. Furthermore, the use of common standards is important as we determine which agents should progress to randomized trials which will use survival as an end point.
CT Check Tags: Human; Male

Androgens: ME, metabolism
*Clinical Trials, Phase II: ST, standards
*Consensus Development Conferences, NIH
Guidelines
*Patient Selection
*Prostate-Specific Antigen: BL, blood
***Prostatic Neoplasms: PA, pathology**
Prostatic Neoplasms: TH, therapy
Reference Values
United States
CN 0 (Androgens); EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 40 OF 78 CANCERLIT on STN
AN 1999446868 CANCERLIT
DN 99446868 PubMed ID: 10519379
TI Response of prostate cancer to anti-Her-2/neu antibody in androgen-dependent and -independent human xenograft models.
AU Agus D B; Scher H I; Higgins B; Fox W D; Heller G; Fazzari M; Cordon-Cardo C; Golde D W
CS Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.. d-agus@ski.mskcc.org
SO CANCER RESEARCH, (1999 Oct 1) 59 (19) 4761-4.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 1999446868
EM 199911
ED Entered STN: 20000221
Last Updated on STN: 20000221
AB Antibody to the Her-2/neu gene product has been shown to inhibit the growth of breast cancer cells overexpressing Her-2/neu and to have clinical utility in treating breast cancer. We studied a recombinant, humanized anti-Her-2/neu antibody (Herceptin) in preclinical models of human prostate cancer. The androgen-dependent CWR22 and LNCaP human prostate cancer xenograft models and **androgen-independent** sublines of CWR22 were used. Her-2/neu staining of the parental, androgen-dependent, and **androgen-independent** CWR22 tumors and LNCaP tumors demonstrated variable Her-2/neu expression. Herceptin was administered i.p. at a dose of 20 mg/kg twice weekly after the xenograft had been established. No effect of Herceptin on tumor growth was observed in any of the **androgen-independent** tumors; however, significant growth inhibition was observed in both of the androgen-dependent xenograft models, CWR22 (68% growth inhibition at the completion of the experiment; P = 0.03 for trajectories of the average tumor volume of the groups) and LNCaP (89% growth inhibition; P = 0.002). There was a significant increase in prostate-specific antigen (PSA) index (ng PSA/ml serum/mm3 tumor) in Herceptin-treated androgen-dependent groups compared with control (CWR22, 18-fold relative to pretreatment value versus 1.0-fold, P = 0.0001; LNCaP, 2.35-fold relative to pretreatment value versus 0.6-fold, P = 0.001). When paclitaxel (6.25 mg/kg s.c., five times/week) was given to animals with androgen-dependent and -independent tumors, there was growth inhibition in each group. Paclitaxel and Herceptin cotreatment led to greater growth inhibition than was seen for the agents individually. Thus, in these prostate cancer model systems, Herceptin alone has clinical activity only in the androgen-dependent tumor and has at least an additive effect on growth, in combination with paclitaxel, in both androgen-dependent and **androgen-**

independent tumors. Response to Herceptin did not correlate with the PSA levels, because the PSA index markedly increased in the Herceptin-treated group, whereas it remained constant in the control group. These results suggest the utility of Herceptin in the treatment of human prostate cancer.

CT Check Tags: Animal; Female; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*Antibodies, Monoclonal: TU, therapeutic use
*Antineoplastic Agents: TU, therapeutic use
Immunohistochemistry
Mice
Mice, Nude
Paclitaxel: TU, therapeutic use
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**
*Receptor, erbB-2: IM, immunology
Transplantation, Heterologous

RN 33069-62-4 (Paclitaxel)

CN 0 (Antibodies, Monoclonal); 0 (Antineoplastic Agents); 0 (trastuzumab); EC 2.7.11.- (Receptor, erbB-2)

L19 ANSWER 41 OF 78 CANCERLIT on STN

AN 1999413456 CANCERLIT

DN 99413456 PubMed ID: 10485446

TI On the prevention and therapy of prostate cancer by androgen administration.

AU Prehn R T

CS Department of Pathology, University of Washington, Kirkland 98033-5308, USA.

SO CANCER RESEARCH, (1999 Sep 1) 59 (17) 4161-4.
Journal code: 2984705R. ISSN: 0008-5472.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS MEDLINE; Priority Journals

OS MEDLINE 1999413456

EM 199909

ED Entered STN: 19991112
Last Updated on STN: 19991112

AB It has been widely suggested that elevated androgen levels may be critically involved in the genesis of prostate cancer. Despite the dependency of the normal prostate and of most prostatic cancers upon androgens and the fact that tumors can be produced in some rodent models by androgen administration, I will argue that, contrary to prevalent opinion, declining rather than high levels of androgens probably contribute more to human prostate carcinogenesis and that androgen supplementation would probably lower the incidence of the disease. I will also consider the possibility that the growth of **androgen-independent** prostate cancers might be reduced by the administration of androgens.

CT Check Tags: Human; Male
Androgens: PH, physiology
*Androgens: TU, therapeutic use
Phenotype
Prostatic Hyperplasia: ET, etiology
***Prostatic Neoplasms: PC, prevention & control**
Prostatic Neoplasms: TH, therapy

CN 0 (Androgens)

L19 ANSWER 42 OF 78 CANCERLIT on STN
AN 1999314784 CANCERLIT
DN 99314784 PubMed ID: 10408865
TI Proliferation- and apoptosis-associated factors in advanced prostatic carcinomas before and after androgen deprivation therapy: prognostic significance of p21/WAF1/CIP1 expression.
AU Baretton G B; Klenk U; Diebold J; Schmeller N; Lohrs U
CS Institute of Pathology, Ludwig-Maximilians-University, Munich, Germany.
SO BRITISH JOURNAL OF CANCER, (1999 May) 80 (3-4) 546-55.
Journal code: 0370635. ISSN: 0007-0920.
CY SCOTLAND: United Kingdom
DT (CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 1999314784
EM 199907
ED Entered STN: 19990813
Last Updated on STN: 19990813
AB The molecular mechanisms leading to **androgen-independent** growth in prostate cancer (PC) are poorly understood. Androgen deprivation therapy (ADT) results physiologically in a decrease in proliferation and an increase in programmed cell death (PCD)/apoptosis. The aim of our study was to get more insight into these processes in prostatic carcinomas before and after ADT. For this purpose, immunohistologic staining for the androgen receptor (AR) molecule, the Ki-67 antigen, the bcl-2 oncoprotein, the p53 protein and its physiologic effector, p21/WAF1, was performed on archival material. PCD was visualized by enzymatic detection of DNA fragmentation. Specimens from 69 PC patients after ADT were studied in correlation to histopathology and prognosis. In 42 cases, corresponding tumour tissue from the untreated primary tumours could be analysed comparatively. Before ADT, histologic grade was associated with Ki-67 index ($P < 0.0001$, Spearman correlation) and PCD rate ($P < 0.05$, Spearman correlation). Ki-67 index correlated with PCD rate ($P < 0.05$, Spearman correlation) and p21/WAF1 expression ($P < 0.01$, Fisher's exact test). p21/WAF1 expression was the only statistically significant prognostic factor for shorter survival ($P < 0.002$, log-rank test). All p21/WAF1-positive cases showed high Ki-67 index and high histologic grade. After ADT, loss of AR expression was associated with high Ki-67 index, whereas histologic signs of regression correlated negatively with Ki-67 index ($P < 0.001$, Pearson chi2 test). p21/WAF1 expression increased significantly ($P < 0.02$, McNemar test) and correlated with p53 accumulation ($P < 0.0001$, Pearson chi2 test). Most significant prognostic parameter after conventional ADT was high-rate p21/WAF1 expression (> 50% of tumour cells; $P < 0.00001$, log-rank test). This study demonstrates that p21/WAF1 overexpression before and after ADT characterizes a subgroup of advanced PC with paradoxically high proliferation rate and significantly worse clinical outcome. This finding might be clinically useful for planning therapy in these patients.
CT Check Tags: Human; Male; Support, Non-U.S. Gov't
Aged
Aged, 80 and over
*Androgen Antagonists: TU, therapeutic use
*Apoptosis
Cell Division
*Cyclins: BI, biosynthesis
DNA, Neoplasm: ME, metabolism
*Growth Substances: BI, biosynthesis
Immunohistochemistry

Ki-67 Antigen: BI, biosynthesis
Middle Age
*Neoplasms, Hormone-Dependent: ME, metabolism
Neoplasms, Hormone-Dependent: PA, pathology
Neoplasms, Hormone-Dependent: SU, surgery
*Neoplasms, Hormone-Dependent: TH, therapy
Orchiectomy
Prognosis
***Prostatic Neoplasms: ME, metabolism**
Prostatic Neoplasms: PA, pathology
Prostatic Neoplasms: SU, surgery
***Prostatic Neoplasms: TH, therapy**
Protein p53: BI, biosynthesis
Proto-Oncogene Proteins c-bcl-2: BI, biosynthesis
Receptors, Androgen: BI, biosynthesis
CN 0 (Androgen Antagonists); 0 (Cip1 protein); 0 (Cyclins); 0 (DNA, Neoplasm); 0 (Growth Substances); 0 (Ki-67 Antigen); 0 (Protein p53); 0 (Proto-Oncogene Proteins c-bcl-2); 0 (Receptors, Androgen)

L19 ANSWER 43 OF 78 CANCERLIT on STN
AN 1999314759 CANCERLIT
DN 99314759 PubMed ID: 10408840
TI Camptothecin sensitizes **androgen-independent** prostate cancer cells to anti-Fas-induced apoptosis.
AU Costa-Pereira A P; Cotter T G
CS Department of Biochemistry, University College, Ireland.
SO BRITISH JOURNAL OF CANCER, (1999 May) 80 (3-4) 371-8.
Journal code: 0370635. ISSN: 0007-0920.
CY SCOTLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 1999314759
EM 199907
ED Entered STN: 19990813
Last Updated on STN: 19990813
AB Despite expressing both Fas and Fas ligand, DU145 and LNCaP prostate cancer cells were resistant to anti-Fas-induced cell death. Resistance to Fas-mediated cytotoxicity could be overcome in DU145, but not in LNCaP, cells by pretreating cells with sublethal doses of cytotoxic drugs, such as camptothecin. Activated caspases were shown to be required for this cytotoxicity. Indeed, poly(ADP-Ribose) polymerase was shown to be proteolytically cleaved in cells treated with camptothecin plus anti-Fas, but not in cells treated with anti-Fas only. Moreover, pretreatment of cells with ZVAD completely blocked camptothecin-mediated Fas-induced apoptosis. Sensitization of cells to Fas-induced cell death did not involve up-regulation of Fas or FasL, and it was independent of alterations in the cell cycle. Reactive oxygen intermediates (ROI) have been shown to be important mediators of drug-induced apoptosis. Here, we demonstrate that treatment of DU145 cells with camptothecin, anti-Fas, or both, did not alter the intracellular levels of peroxide or superoxide anion.
CT Check Tags: Human; Male; Support, Non-U.S. Gov't
*Androgens: PH, physiology
Antigens, CD95: BI, biosynthesis
*Antigens, CD95: IM, immunology
*Antineoplastic Agents, Phytogenic: PD, pharmacology
*Apoptosis: DE, drug effects
Apoptosis: IM, immunology

*Camptothecin: PD, pharmacology
Caspases: ME, metabolism
Cytotoxicity, Immunologic: DE, drug effects
Enzyme Activation
Immunoglobulin M: PD, pharmacology
Membrane Glycoproteins: BI, biosynthesis
Membrane Glycoproteins: IM, immunology
Mitochondria: PH, physiology
*Neoplasms, Hormone-Dependent: IM, immunology
Neoplasms, Hormone-Dependent: PA, pathology
*Neoplasms, Hormone-Dependent: TH, therapy
***Prostatic Neoplasms: IM, immunology**
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**
Reactive Oxygen Species
Tumor Cells, Cultured
RN 7689-03-4 (Camptothecin)
CN 0 (Androgens); 0 (Antigens, CD95); 0 (Antineoplastic Agents, Phytogenic); 0 (FasL protein); 0 (Immunoglobulin M); 0 (Membrane Glycoproteins); 0 (Reactive Oxygen Species); EC 3.4.22.- (Caspases)

L19 ANSWER 44 OF 78 CANCERLIT on STN
AN 1999289901 CANCERLIT
DN 99289901 PubMed ID: 10361551
TI Serologic tumor markers, clinical biology, and therapy of prostatic carcinoma.
AU Kim J; Logothetis C J
CS Department of Genitourinary Oncology, University of Texas M. D. Anderson Cancer Center, Houston, USA.
SO UROLOGIC CLINICS OF NORTH AMERICA, (1999 May) 26 (2) 281-90. Ref: 92
Journal code: 0423221. ISSN: 0094-0143.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS MEDLINE; Abridged Index Medicus Journals; Priority Journals
OS MEDLINE 1999289901
EM 199906
ED Entered STN: 19990709
Last Updated on STN: 19990709
AB PSA has been a valuable tool in enhancing our understanding of the prevalence and virulence of prostate cancer. PSA also has contributed to the understanding of important phenomena related to the androgen regulation of the cancer; however, it has not been useful in detecting some forms of **androgen-independent** (neuroendocrine) progression and is of limited prognostic value in **androgen-independent** prostate cancer. PSA also has been valuable in the accelerated development of therapies for prostate cancer; however, it must be used cautiously for this purpose, because it may not reflect the most relevant clone. In addition, some agents may directly affect PSA release independent of their antitumor activity. Most importantly, before PSA is adopted as a surrogate end point in clinical trials in prostate cancer, it must be prospectively validated. Future studies must focus on the development of prospective serologic tumor markers that can predict virulence of disease and to reflect **androgen-independent** progression.
CT Check Tags: Human; Male
Androgen Antagonists: TU, therapeutic use

Antineoplastic Agents: TU, therapeutic use
Orchiectomy
Prognosis
*Prostate-Specific Antigen: BL, blood
***Prostatic Neoplasms: DI, diagnosis**
***Prostatic Neoplasms: TH, therapy**
Sesquiterpenes: TU, therapeutic use
Suramin: TU, therapeutic use
RN 129298-91-5 (O-(chloroacetylcarbamoyl)fumagillol); 145-63-1 (Suramin)
CN 0 (Androgen Antagonists); 0 (Antineoplastic Agents); 0 (Sesquiterpenes); EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 45 OF 78 CANCERLIT on STN
AN 1999289899 CANCERLIT
DN 99289899 PubMed ID: 10361549
TI The biology of hormone refractory prostate cancer. Why does it develop?.
AU Isaacs J T
CS Department of Oncology, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA.
NC R01 DK52645 (NIDDK)
SO UROLOGIC CLINICS OF NORTH AMERICA, (1999 May) 26 (2) 263-73. Ref: 38
Journal code: 0423221. ISSN: 0094-0143.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS MEDLINE; Abridged Index Medicus Journals; Priority Journals
OS MEDLINE 1999289899
EM 199906
ED Entered STN: 19990709
Last Updated on STN: 19990709
AB Androgen ablation therapy has been an important modality for the treatment of disseminating prostatic cancer for nearly 60 years. Unfortunately, when given alone, such therapy is rarely curative. The failure of this therapy to cure prostate tumors, even though it can induce an initially positive response, is not the result of a change in the systemic effectiveness of such treatment. Instead, the development of resistance to therapy is related to changes in the tumor. Experiments by a large number of investigators have identified several of the important tumor cell and host factors involved in these changes. Through the identification of these factors, the concept has evolved that there may be multiple pathways for the development of resistance to hormonal therapy based on a stem cell model for the normal prostate. Although such pathways can be described in phenomenological terms, the detailed molecular biology of such a process is still unknown. The essential feature of the development of androgen resistance is the emergence of **androgen-independent** or sensitive cancer cells. The critical question for that must be answered by future studies is exactly how such **androgen-independent** cells develop. An explanation may make it possible to design therapies to prevent the development of these independent tumor cells. Under such conditions, androgen ablation therapy used as a single modality could become potentially curative. Even if therapeutic means can be developed to prevent the emergence of **androgen-independent** or sensitive tumor cells, to be effective, this type of blocking therapy would have to be performed before such development had already occurred. Therefore, before such therapy is begun, some type of clinical test would be required to determine that the tumor did not already have some **androgen-independent** or sensitive tumor cells present

(i.e., the tumor was not already heterogeneous androgen-sensitive). Because, currently, neither a method for determining the homogeneous versus heterogeneous nature of the androgen requirements of a particular tumor nor a method for the prevention of the development of **androgen-independent** or sensitive tumor cells from dependent prostate cancer cells is available, these should be critical areas for extensive future study. Any advancement in either of these areas would have profound consequences on the more effective issue of androgen ablation therapy. Until these advancements are made, androgen ablation therapy can be used in combination with other modalities of treatment (e.g., radiation and chemotherapy), which are specifically targeted at the **androgen-independent** or sensitive cells either initially present or developing during androgen ablation therapy. Standard antiproliferative chemotherapeutic agents may be ineffective against such **androgen-independent** or sensitive prostatic cancers because these cancers have a low proliferative rate. Berges and co-workers demonstrated that the median daily proliferative rate of prostate cancer cells within lymph nodes or bone metastases was less than 3.0% per day. Newer agents are needed to target the greater than 95% of prostate cancer cells within a given metastatic site that are not immediately proliferating. One such approach that has been recently proposed is the use of potent and selective inhibitors of the endoplasmic reticulum Ca2+ ATP-dependent pump. In such combination approaches, it will be critical to evaluate the importance of both the timing (early versus late) and the order (sequential versus simultaneous) of androgen therapy in relation to the other modalities used.

CT Check Tags: Human; Male; Support, U.S. Gov't, P.H.S.
Androgen Antagonists: TU, therapeutic use
*Androgens: PH, physiology
Neoplasms, Hormone-Dependent: PP, physiopathology
Orchiectomy
Prostate: PA, pathology
Prostate: PH, physiology
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: PP, physiopathology**
Prostatic Neoplasms: TH, therapy
Treatment Failure

CN 0 (Androgen Antagonists); 0 (Androgens)

L19 ANSWER 46 OF 78 CANCERLIT on STN
AN 1999274546 CANCERLIT
DN 99274546 PubMed ID: 10344749
TI Sustained in vivo regression of Dunning H rat prostate cancers treated with combinations of androgen ablation and Trk tyrosine kinase inhibitors, CEP-751 (KT-6587) or CEP-701 (KT-5555).
AU George D J; Dionne C A; Jani J; Angeles T; Murakata C; Lamb J; Isaacs J T
CS Johns Hopkins University, Baltimore, Maryland 21231, USA.
SO CANCER RESEARCH, (1999 May 15) 59 (10) 2395-401.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 1999274546
EM 199906
ED Entered STN: 19990709
Last Updated on STN: 19990709
AB The indolocarbazole analogue CEP-751 is a potent and selective tyrosine kinase inhibitor of the neurotrophin-specific trk receptors that has

demonstrated antitumor activity in nine different models of prostate cancer growth in vivo. In the slow-growing, androgen-sensitive Dunning H prostate cancers, which express trk receptors, CEP-751 induced transient regressions independent of effects on cell cycle. Because androgen ablation is the most commonly used treatment for prostate cancer, we examined whether the combination treatment of CEP-751 with castration would lead to better antitumor efficacy than either treatment alone. For a 60-day period, H tumor-bearing rats received treatment with either castration, CEP-751 (10 mg/kg once a day s.c. for 5 days every 2 weeks), a combination of both, or vehicle. Castration caused tumor regression, followed by tumor regrowth in 4-6 weeks, whereas intermittent CEP-751 treatments resulted in tumor regressions during each treatment, which were followed by a period of regrowth between intermittent drug treatment cycles. Overall, both monotherapies significantly inhibited tumor growth compared with the vehicle-treated control group. However, the combination of castration and concomitant CEP-751 produced the most dramatic results: sigificantly greater tumor regression than either therapy alone, with no signs of regrowth. A related experiment using an orally administered CEP-751 analogue (CEP-701), as the trk inhibitor, and a gonadotrophin-releasing hormone agonist, Leuprolide, to induce androgen ablation demonstrated similar results, indicating that these effects could be generalized to other forms of androgen ablation and other trk inhibitors within this class. In addition, when CEP-701 was given sequentially to rats bearing H tumors, which were progressing in the presence of continuous androgen ablation induced by Leuprolide, regression of the **androgen-independent** tumors occurred. In summary, these data demonstrate that CEP-751 or CEP-701, when combined with surgically or chemically induced androgen ablation, offer better antitumor efficacy than either monotherapy and suggest that each therapy produces prostate cancer cell death through complementary mechanisms.

CT Check Tags: Animal; Comparative Study; Male; Support, Non-U.S. Gov't
*Adenocarcinoma: DT, drug therapy
Adenocarcinoma: PA, pathology
Adenocarcinoma: TH, therapy
Administration, Oral
*Androgens
Antineoplastic Agents: AD, administration & dosage
*Antineoplastic Agents: TU, therapeutic use
*Antineoplastic Agents, Hormonal: TU, therapeutic use
Carbazoles: AD, administration & dosage
*Carbazoles: TU, therapeutic use
Combined Modality Therapy
Drug Screening Assays, Antitumor
Drug Synergism
Injections, Subcutaneous
*Leuprolide: TU, therapeutic use
*Neoplasm Proteins: AI, antagonists & inhibitors
Neoplasm Proteins: BI, biosynthesis
Neoplasm Proteins: GE, genetics
Neoplasm Transplantation
*Neoplasms, Hormone-Dependent: DT, drug therapy
Neoplasms, Hormone-Dependent: PA, pathology
Neoplasms, Hormone-Dependent: TH, therapy
*Orchiectomy
***Prostatic Neoplasms: DT, drug therapy**
Prostatic Neoplasms: PA, pathology
Prostatic Neoplasms: TH, therapy
*Proto-Oncogene Proteins: AI, antagonists & inhibitors
Proto-Oncogene Proteins: BI, biosynthesis

Proto-Oncogene Proteins: GE, genetics
Rats
*Receptor Protein-Tyrosine Kinases: AI, antagonists & inhibitors
Receptor Protein-Tyrosine Kinases: BI, biosynthesis
Receptor Protein-Tyrosine Kinases: GE, genetics
Receptor, trkA
*Receptors, Nerve Growth Factor: AI, antagonists & inhibitors
Receptors, Nerve Growth Factor: BI, biosynthesis
Receptors, Nerve Growth Factor: GE, genetics
RN 53714-56-0 (Leuprolide)
CN 0 (Androgens); 0 (Antineoplastic Agents); 0 (Antineoplastic Agents, Hormonal); 0 (CEP 701); 0 (CEP 751); 0 (Carbazoles); 0 (Neoplasm Proteins); 0 (Proto-Oncogene Proteins); 0 (Receptors, Nerve Growth Factor); EC 2.7.11.- (Receptor Protein-Tyrosine Kinases); EC 2.7.11.- (Receptor, trkA)

L19 ANSWER 47 OF 78 CANCERLIT on STN
AN 1999259151 CANCERLIT
DN 99259151 PubMed ID: 10328599
TI Advances in prostate cancer.
AU Small E J
CS University of California, San Francisco, Mount Zion Cancer Center, 94115, USA.
SO CURRENT OPINION IN ONCOLOGY, (1999 May) 11 (3) 226-35. Ref: 73
Journal code: 9007265. ISSN: 1040-8746.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 1999259151
EM 199906
ED Entered STN: 19990813
Last Updated on STN: 19990813
AB The causes of prostate cancer reflect a complex interaction between environmental and genetic factors. Improvement in screening has reduced the incidence of prostate cancer, and risk assessment schemata have enhanced therapy, both for localized disease and for locally recurrent prostate cancer. The use of hormone therapy has been further evaluated, as primary therapy for locally advanced cancers, for lymph node-positive cancers, and for de novo metastatic cancer. Modest inroads have been made in the treatment and understanding of **androgen-independent** prostate cancer. Advances have been made in the understanding of the risk factors, genetic and environmental, associated with the development and progression of prostate cancer; in screening; and in optimizing therapy for localized, locally recurrent, and advanced disease. This article reviews the most salient observations reported between November 1, 1997 and October 31, 1998.
CT Check Tags: Human; Male
Aged
Mass Screening
Middle Age
Prostate-Specific Antigen: BL, blood
Prostatectomy
Prostatic Neoplasms: DI, diagnosis
***Prostatic Neoplasms: EP, epidemiology**
Prostatic Neoplasms: PC, prevention & control
***Prostatic Neoplasms: TH, therapy**

Radiotherapy, Conformal
CN EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 48 OF 78 CANCERLIT on STN
AN 1999170992 CANCERLIT
DN 99170992 PubMed ID: 10071598
TI Treatment options in **androgen-independent** prostate cancer.
AU Lara P N Jr; Meyers F J
CS University of California Davis Cancer Center, Division of Hematology-Oncology, Sacramento, California, USA.
SO CANCER INVESTIGATION, (1999) 17 (2) 137-44. Ref: 72
Journal code: 8307154. ISSN: 0735-7907.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 1999170992
EM 199903
ED Entered STN: 19990428
Last Updated on STN: 19990428
AB Metastatic prostate cancer is a leading cause of cancer-related death in men. Although most patients will respond to androgen ablation as initial systemic therapy, nearly all patients will develop **androgen-independent** prostate cancer (AI CaP) and will succumb to the disease. Advances in molecular biology have demonstrated mutations in and persistent expression of the human androgen receptor in metastatic disease. Furthermore, recent evidence indicates that an apoptotic block through p53 mutations or bcl-2 overexpression may have a potential role in the poor responses seen with standard chemotherapy. Presently, the six general treatment options available for AI CaP are best supportive care, radiation therapy, radioisotopes, secondline hormonal therapy, chemotherapy (single agent or combination), and investigational therapies such as monoclonal antibodies, cyclin-dependent kinase inhibitors, matrix metalloproteinase inhibitors, and antiangiogenesis agents, among others. None of these modalities have produced durable remissions, although some have demonstrated palliative benefit. The next generation of clinical trials should not consist of futile hormonal manipulations or repetitive chemotherapy. Therapeutic strategies aimed at circumventing molecular blocks to cell death or targeting unique cancer molecules and genes will be more likely to improve quality of life and longevity. Furthermore, the aggressive use of palliative care will ensure effective caring for patients and the healing of families in the absence of cure.
CT Check Tags: Human; Male; Support, U.S. Gov't, Non-P.H.S.
Adenocarcinoma: DT, drug therapy
Adenocarcinoma: PA, pathology
Adenocarcinoma: SC, secondary
*Adenocarcinoma: TH, therapy
Androgen Antagonists: TU, therapeutic use
*Androgens
Antibodies, Monoclonal: TU, therapeutic use
Antineoplastic Agents: TU, therapeutic use
Antineoplastic Agents, Hormonal: TU, therapeutic use
Antineoplastic Combined Chemotherapy Protocols: TU, therapeutic use
Apoptosis
Bone Neoplasms: RT, radiotherapy
Bone Neoplasms: SC, secondary

Bone Neoplasms: TH, therapy
Clinical Trials
Combined Modality Therapy
Drug Design
Gonadorelin: AG, agonists
Neoplasm Metastasis
Neoplasms, Hormone-Dependent: DT, drug therapy
Neoplasms, Hormone-Dependent: PA, pathology
*Neoplasms, Hormone-Dependent: TH, therapy
Orchiectomy
Palliative Care
Prostatectomy
Prostatic Neoplasms: DT, drug therapy
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**
Radioisotopes: TU, therapeutic use
Radiotherapy: MT, methods
Receptors, Growth Factor: DE, drug effects
Suramin: PD, pharmacology
Suramin: TU, therapeutic use
RN 145-63-1 (Suramin); 33515-09-2 (Gonadorelin)
CN 0 (Androgen Antagonists); 0 (Androgens); 0 (Antibodies, Monoclonal); 0 (Antineoplastic Agents); 0 (Antineoplastic Agents, Hormonal); 0 (Antineoplastic Combined Chemotherapy Protocols); 0 (Radioisotopes); 0 (Receptors, Growth Factor)

L19 ANSWER 49 OF 78 CANCERLIT on STN
AN 1999154706 CANCERLIT
DN 99154706 PubMed ID: 10037102
TI Post-therapy serum prostate-specific antigen level and survival in patients with **androgen-independent** prostate cancer.
AU Scher H I; Kelly W M; Zhang Z F; Ouyang P; Sun M; Schwartz M; Ding C; Wang W; Horak I D; Kremer A B
CS Department of Medicine, Memorial Sloan-Kettering Cancer Center, and Cornell University Medical College, New York, NY 10021, USA.
NC CA05826 (NCI)
CA09207 (NCI)
SO JOURNAL OF THE NATIONAL CANCER INSTITUTE, (1999 Feb 3) 91 (3) 244-51. Journal code: 7503089. ISSN: 0027-8874.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 1999154706
EM 199903
ED Entered STN: 19990428
Last Updated on STN: 19990428
AB BACKGROUND: With an hypothesis that post-chemotherapy changes in serum prostate-specific antigen (PSA) levels might serve as a surrogate marker for assessing prostate cancer outcome (i.e., survival), we studied the relationship between pretherapy and post-therapy prognostic factors and survival in patients with **androgen-independent** prostate cancer. METHODS: A prognostic model for survival based on pretherapy and post-therapy parameters was developed from the clinical data on 254 patients with **androgen-independent** prostate cancer treated with 11 different protocol therapies at Memorial Sloan-Kettering Cancer Center. The model was validated by use of an independent dataset of 541 patients enrolled in two randomized phase III trials. RESULTS: In multivariate analysis, a post-therapy decline in PSA

levels of 50% achieved in 12 weeks was a statistically significant factor associated with survival (two-sided P = .0012). A similar outcome was obtained with the use of an 8-week time frame. Elevated pretherapy level of serum lactate dehydrogenase (two-sided P = .0001), lower pretherapy level of hemoglobin (P = .0001), and younger age (two-sided P = .0430) had a statistically significant negative impact on outcome. Median survival times were 23, 17, and 9 months for low-, intermediate-, and high-risk groups of patients defined by the prognostic model, respectively. CONCLUSION: This study confirms the prognostic value of a post-therapy decline in PSA of 50% or greater from baseline in relation to survival in patients with **androgen-independent** prostate cancer treated with a variety of therapies. Two consecutive determinations at 4-week intervals can be used as an end point for efficacy in phase II trials of therapies in this disease.

CT Check Tags: Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Aged
Aged, 80 and over
Middle Age
Multivariate Analysis
Prognosis
*Prostate-Specific Antigen: BL, blood
***Prostatic Neoplasms: IM, immunology**
Prostatic Neoplasms: TH, therapy
Reproducibility of Results
Risk Factors
Survival Analysis

CN EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 50 OF 78 CANCERLIT on STN
AN 1999124221 CANCERLIT
DN 99124221 PubMed ID: 9927031
TI Activation of mitogen-activated protein kinase associated with prostate cancer progression.
AU Gioeli D; Mandell J W; Petroni G R; Frierson H F Jr; Weber M J
CS Department of Microbiology and Cancer Center, University of Virginia Health Sciences Center, Charlottesville 22908, USA.
NC CA39076 (NCI)
CA76500 (NCI)
GM47332 (NIGMS)
+
SO CANCER RESEARCH, (1999 Jan 15) 59 (2) 279-84.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 1999124221
EM 199902
ED Entered STN: 19990405
Last Updated on STN: 19990405
AB Using an antibody specific for dually phosphorylated extracellular-regulated kinases 1 and 2, we have examined 82 primary and metastatic prostate tumor specimens for the presence of activated mitogen-activated protein (MAP) kinase. Nonneoplastic prostate tissue showed little or no staining with activated MAP kinase antiserum. In prostate tumors, the level of activated MAP kinase increased with increasing Gleason score and tumor stage. In a separate analysis, tumor samples from two patients showed no activation of MAP kinase before androgen ablation therapy;

however, following androgen ablation treatment, high levels of activated MAP kinase were detected in the recurrent tumors. Collectively, these data suggest an increase in the activation of the MAP kinase signal transduction pathway as prostate cancer progresses to a more advanced and **androgen-independent** disease.

CT Check Tags: Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*Ca(2+)-Calmodulin Dependent Protein Kinase: ME, metabolism
Enzyme Activation
Immunohistochemistry
Neoplasm Staging
***Prostatic Neoplasms: EN, enzymology**
Prostatic Neoplasms: PA, pathology
Prostatic Neoplasms: TH, therapy
Signal Transduction
p42 MAP Kinase

CN EC 2.7.10.- (Ca(2+)-Calmodulin Dependent Protein Kinase); EC 2.7.10.- (extracellular signal-regulated kinase 1); EC 2.7.10.- (p42 MAP Kinase)

L19 ANSWER 51 OF 78 CANCERLIT on STN
AN 1998357533 CANCERLIT
DN 98357533 PubMed ID: 9694160
TI In vivo gene therapy for prostate cancer: preclinical evaluation of two different enzyme-directed prodrug therapy systems delivered by identical adenovirus vectors.
AU Martiniello-Wilks R; Garcia-Aragon J; Daja M M; Russell P; Both G W; Molloy P L; Lockett L J; Russell P J
CS Oncology Research Centre, Prince of Wales Hospital, Randwick, NSW, Australia.
SO HUMAN GENE THERAPY, (1998 Jul 20) 9 (11) 1617-26.
Journal code: 9008950. ISSN: 1043-0342.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 1998357533
EM 199810
ED Entered STN: 19990122
Last Updated on STN: 19990122
AB Advanced prostate cancer is invariably lethal once it becomes **androgen independent** (AI). With the aim of developing a new treatment we have used the human **androgen-independent** prostate cancer cell line, PC-3, to evaluate the effectiveness of two enzyme-directed prodrug therapy (EPT) systems as a novel means for promoting tumor cell destruction in vivo. We have confined our study to the use of a PSA promoter, in a preliminary attempt to achieve prostate specificity. The two EPT systems used were the HSVTK/GCV and PNP/6MPDR systems. These were chosen for their differential dependence on DNA replication for their mechanism of action. In the present work, either the HSVTK or PNP gene, each controlled by a PSA promoter fragment, was delivered by an E1-, replication-deficient human adenovirus (Ad5) into PC-3 tumors growing subcutaneously in BALB/c nude mice. Tumors were injected with a single dose of recombinant Ad5 and mice were treated intraperitoneally with the appropriate prodrug, twice daily, for 6 days thereafter. The growth of established PC-3 tumors was significantly suppressed and host survival increased with a single course of HSVTK/GCV or PNP/6MPDR treatment. HSVTK/GCV-treated PC-3 tumor growth was 80% less than that of control treatments on day 33, while PNP/6MPDR-treated tumor growth was approximately 75% less than that of control treatments on day

52. Survival data showed that 20% of HSVTK/GCV- or PNP/6MPDR-treated animals lived >45 and >448 days, respectively, longer than control animals. These results demonstrate that both HSVTK/GCV and PNP/6MPDR therapies interrupt the growth of an aggressive human prostate cancer cell line in vivo.

CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't
*Adenocarcinoma: TH, therapy
*Adenoviridae: GE, genetics
Escherichia coli: EN, enzymology
Ganciclovir: PD, pharmacology
*Gene Therapy
Genetic Vectors
Mice
Mice, Inbred BALB C
Mice, Nude
*Prodrugs: PD, pharmacology
***Prostatic Neoplasms: TH, therapy**
*Purine-Nucleoside Phosphorylase: GE, genetics
Purine-Nucleoside Phosphorylase: ME, metabolism
Simplexvirus: EN, enzymology
*Thymidine Kinase: GE, genetics
Thymidine Kinase: ME, metabolism
Tumor Cells, Cultured

RN 82410-32-0 (Ganciclovir)

CN 0 (Genetic Vectors); 0 (Prodrugs); EC 2.4.2.1 (Purine-Nucleoside Phosphorylase); EC 2.7.1.21 (Thymidine Kinase)

L19 ANSWER 52 OF 78 CANCERLIT on STN

AN 1998290618 CANCERLIT

DN 98290618 PubMed ID: 9628654

TI Development of prostate-specific antigen promoter-based gene therapy for **androgen-independent** human prostate cancer.

AU Gotoh A; Ko S C; Shirakawa T; Cheon J; Kao C; Miyamoto T; Gardner T A; Ho L J; Cleutjens C B; Trapman J; Graham F L; Chung L W

CS Department of Urology, Molecular Urology and Therapeutics Program, University of Virginia, Charlottesville 22908, USA.

NC 1R29CA74042-01 (NCI)

SO JOURNAL OF UROLOGY, (1998 Jul) 160 (1) 220-9.
Journal code: 0376374. ISSN: 0022-5347.

CY United States

DT Journal; Article; (JOURNAL ARTICLE)

LA English

FS MEDLINE; Abridged Index Medicus Journals; Priority Journals

OS MEDLINE 1998290618

EM 199807

ED Entered STN: 19980805
Last Updated on STN: 19980805

AB PURPOSE: The goal of this study is to develop a tissue-specific toxic gene therapy utilizing the prostate specific antigen (PSA) promoter for both androgen-dependent (AD) and **androgen-independent** (AI) PSA-secreting prostate cancer cells. Ideally this gene therapy would be effective without the necessity of exposing the target cells to circulating androgens. MATERIALS AND METHODS: An AI subline of LNCaP, an AD PSA-secreting human prostate cancer cell line, C4-2, was used in this study. Castrated mice bearing C4-2 tumors secrete PSA. A transient expression experiment was used to analyze the activity of two PSA promoters, a 5837 bp long PSA promoter and a 642 bp short PSA promoter, in C4-2 cells. A recombinant adenovirus (Ad-PSA-TK) carrying thymidine kinase under control of the long PSA promoter was generated. The tissue-specific

activity of Ad-PSA-TK was tested in vitro and in vivo. RESULTS: The long PSA promoter had superior activity over short PSA promoter, and higher activity in C4-2 cells than in LNCaP cells. High activity of Ad-PSA-TK was observed in C4-2 cells in an androgen deprived condition. In vitro, Ad-PSA-TK was further demonstrated to induce marked C4-2 cell-kill by acyclovir in medium containing 5% FBS. No cell-kill was observed in control WH cells (a human bladder cancer cell line). In vivo, Ad-PSA-P-TK with acyclovir significantly inhibited subcutaneous C4-2 tumor growth and PSA production in castrated animals. CONCLUSION: The 5837 bp long PSA promoter was active in the androgen free environment and could be used to target both androgen-dependent and independent PSA-producing prostate cancer cells in vitro, and prostate tumors in castrated hosts.

CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Adenoviridae: GE, genetics
*Gene Therapy
Mice
Prostate-Specific Antigen: BI, biosynthesis
*Prostate-Specific Antigen: GE, genetics
Prostatic Neoplasms: ME, metabolism
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**
Recombination, Genetic
Species Specificity
Thymidine Kinase: BI, biosynthesis
Thymidine Kinase: GE, genetics
Transfection
Tumor Cells, Cultured

CN EC 2.7.1.21 (Thymidine Kinase); EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 53 OF 78 CANCERLIT on STN
AN 1998246023 CANCERLIT
DN 98246023 PubMed ID: 9586611
TI Neuroendocrine differentiation in prostatic carcinoma during hormonal treatment.
AU Jiborn T; Bjartell A; Abrahamsson P A
CS Department of Urology, University Hospital, Malmo, Sweden.
SO UROLOGY, (1998 Apr) 51 (4) 585-9.
Journal code: 0366151. ISSN: 0090-4295.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 1998246023
EM 199806
ED Entered STN: 19980713
Last Updated on STN: 19980713
AB OBJECTIVES: Neuroendocrine differentiation (NED) is a common feature in adenocarcinoma of the prostate. Several studies suggest that NED may have a major impact on cancer progression as neuroendocrine (NE) secretory products have been shown to possess growth stimulatory effects. NED has also been proposed to constitute part of the mechanism by which a prostate cancer cell progresses toward androgen independence as NE tumor cells have been demonstrated to be devoid of androgen receptor immunoreactivity. In this retrospective study, we evaluated NED status in prostate cancer specimens from patients undergoing androgen ablation therapy. METHODS: The degree of NED in transurethral resection of the prostate (TURP) samples from 53 patients with prostate cancer was investigated by immunocytochemistry using polyclonal rabbit immunoglobin G (IgG) against

chromogranin A (CgA). Changes in NED with time were determined by a manual semiquantitative cell counting method. RESULTS: During androgen withdrawal therapy, 21 tumors (40%) displayed increased NED concomitant with histopathologic tumor progression, whereas 29 carcinomas (55%) showed no change in NED status. However, a majority of the histopathologically unchanged tumors displayed marked NED at the first TURP and an increase in NED was by definition not possible. In only 3 cases (5%) was a decrease in NED observed with time. CONCLUSIONS: Androgen ablation therapy may be a contributing factor to the increase in NED of prostatic adenocarcinoma with time, and our findings imply that androgen withdrawal therapy enhances the selection and progression of NED, **androgen-independent** tumor cells.

CT Check Tags: Human; Male
*Adenocarcinoma: PA, pathology
*Adenocarcinoma: TH, therapy
Aged
Aged, 80 and over
Follow-Up Studies
Middle Age
Neuroendocrine Tumors: PA, pathology
Orchiectomy
***Prostatic Neoplasms: PA, pathology**
***Prostatic Neoplasms: TH, therapy**

L19 ANSWER 54 OF 78 CANCERLIT on STN
AN 1998192203 CANCERLIT
DN 98192203 PubMed ID: 9533532
TI Interferon-gamma and monoclonal antibody 131I-labeled CC49: outcomes in patients with **androgen-independent** prostate cancer.
AU Slovin S F; Scher H I; Divgi C R; Reuter V; Sgouros G; Moore M; Weingard K; Pettengall R; Imbriaco M; El-Shirbiny A; Finn R; Bronstein J; Brett C; Milenic D; Dnistrian A; Shapiro L; Schlom J; Larson S M
CS Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, New York 10021, USA.
NC CA05826 (NCI)
CA09512 (NCI)
SO CLINICAL CANCER RESEARCH, (1998 Mar) 4 (3) 643-51.
Journal code: 9502500. ISSN: 1078-0432.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 1998192203
EM 199805
ED Entered STN: 19980610
Last Updated on STN: 19980610
AB To assess the tumor targeting, safety, and efficacy of monoclonal antibody 131I-labeled CC49 in patients with **androgen-independent** prostate cancer, 16 patients received 75 mCi/m2 of the radiolabeled antibody after 7 days of IFN-gamma pretreatment. Sequential tumor biopsies in three patients showed a median 5-fold (range, 2-6-fold) increase in the proportion of cells staining positively for the TAG-72 antigen, whereas one showed a decrease in staining. Fourteen patients received 131I-labeled CC49, whereas 2 showed a disease-related decrease in performance status, precluding antibody treatment. The antibody localized to sites of metastatic **androgen-independent** prostate cancer in 86% (12 of 14; 95% confidence interval, 57-95%) of cases. Both osseous and extraosseous sites were visualized, and in six (42%) patients, more areas were visible when the radioimmunoconjugate was used than were apparent

when conventional scanning techniques were used. The localization of the conjugate in the marrow cavity was usually a site not visualized by the radionuclide bone scan, in which the isotope localizes primarily to the tumor-bone interface. The dose-limiting toxicity was thrombocytopenia because five (36%) patients showed grade IV and seven (50%) showed grade III effects. In addition, six (42%) patients, four of whom were hospitalized, showed a flare in baseline pain, and four showed a decrease in pain. No patient showed a >50% decline in prostate-specific antigen, although radionuclide bone scans remained stable in four cases for a median of 4 months. The results are consistent with dosimetry estimates showing that the delivered dose to tumor was subtherapeutic and suggest that approaches that exclusively target the bone tumor interface or the marrow stroma may be unable to completely eradicate disease in the marrow cavity. For CC49, improving outcomes would require repetitive dosing, which was precluded by the rapid development of a human antimouse antibody response.

CT Check Tags: Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Aged
Aged, 80 and over
Antibodies, Monoclonal
Antigens, Neoplasm: AN, analysis
Bone Marrow: IM, immunology
Bone Marrow: PA, pathology
Bone and Bones: RI, radionuclide imaging
Combined Modality Therapy
Glycoproteins: AN, analysis
*Interferon Type II: TU, therapeutic use
*Iodine Radioisotopes: TU, therapeutic use
Middle Age
Neoplasms, Hormone-Dependent: PA, pathology
Neoplasms, Hormone-Dependent: RT, radiotherapy
*Neoplasms, Hormone-Dependent: TH, therapy
Pain
Prostate-Specific Antigen: BL, blood
Prostatic Neoplasms: PA, pathology
Prostatic Neoplasms: RI, radionuclide imaging
Prostatic Neoplasms: RT, radiotherapy
***Prostatic Neoplasms: TH, therapy**
*Radioimmunotherapy
Tomography, Emission-Computed
Tomography, Emission-Computed, Single-Photon
Treatment Outcome

RN 82115-62-6 (Interferon Type II)

CN 0 (Antibodies, Monoclonal); 0 (Antigens, Neoplasm); 0 (Glycoproteins); 0 (Iodine Radioisotopes); 0 (tumor-associated antigen 72); EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 55 OF 78 CANCERLIT on STN

AN 1998098359 CANCERLIT

DN 98098359 PubMed ID: 9436028

TI Human prostate cancer progression models and therapeutic intervention.

AU Chung L W; Kao C; Sikes R A; Zhau H E

CS Department of Urology, University of Virginia Health Sciences Center, Charlottesville, USA.

NC RO1 CA64863 (NCI)

SO HINYOKIKA KIYO. ACTA UROLOGICA JAPONICA, (1997 Nov) 43 (11) 815-20. Ref: 12
Journal code: 0421145. ISSN: 0018-1994.

CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 1998098359
EM 199802
ED Entered STN: 19980417
Last Updated on STN: 19980417
AB Our laboratory has developed two cellular models of human prostate cancer progression. The LNCaP prostate cancer progression model is based upon the well-known cellular interaction between human prostate or bone stromal cells and LNCaP cells in vivo. The marginally tumorigenic LNCaP cells acquired tumorigenic and metastatic potential upon cellular interaction with either prostate or bone fibroblasts. A subline termed C4-2 was observed to grow readily in castrated animals and acquired metastatic potential spreading from the primary tumor site to the lymph node, the seminal vesicles, and the axial skeleton, resulting in an intense osteoblastic reaction. The second model is ARCaP, where prostate cancer cells derived from the ascites fluid of a man with metastatic disease exhibited an Androgen- and estrogen-Repressed Prostate Cancer cell growth and tumor formation in either a hormone-deficient or a castrated environment. However, the growth of either the tumor cells in vitro or the tumors in vivo was suppressed by both estrogen and androgen. While the tumor cells expressed low levels of androgen receptor and prostate-specific antigen (PSA), they were highly metastatic when inoculated orthotopically. Distant metastases to a number of organs were detected, including the liver, lung, kidney, and bone. We have employed a human prostate cancer progression model as a system to study the efficacy of gene therapy. Results of the study show that whereas universal promoters, such as Cytomegalovirus (CMV) and Rous Sarcoma Virus (RSV) promoter-driven tumor suppressors (e.g. p53, p21, and p16), were effective in inhibiting prostate tumor growth, the advantages of driving the expression of therapeutic toxic genes using a tissue-specific promoter prostate-specific antigen (PSA) and a tumor--but not tissue-specific promoter, osteocalcin (OC), are preferred. In the case of the PSA promoter, we can achieve cell-kill in PSA-producing human prostate cancer cells. To circumvent the supporting role of bone stroma for prostate cancer epithelial growth, we have recently developed a novel concept where the expression of therapeutic toxic genes is driven by a tumor--but not a tissue-specific OC promoter. Osteocalcin-thymidine kinase (OC-TK) was found to efficiently eradicate the growth of osteosarcoma, prostate, and brain tumors both in vitro and in vivo. We observed that **androgen -independent** human prostate cancer cells lines expressed OC-TK at higher levels than androgen-dependent human prostate cancer cell lines. We have obtained data to suggest that Ad-OC-TK plus a pro-drug acyclovir (ACV) may be used as an effective therapy to treat prostate cancer bone metastasis in models where the growth of **androgen-independent** PC-3 and C4-2 tumors in the bone has occurred.
CT Check Tags: Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Acyclovir: TU, therapeutic use
Androgens: ME, metabolism
Disease Models, Animal
Disease Progression
*Gene Therapy
Osteocalcin: GE, genetics
Osteocalcin: TU, therapeutic use

Prodrugs: TU, therapeutic use
Promoter Regions (Genetics)
Prostate-Specific Antigen: GE, genetics
*Prostatic Neoplasms
Prostatic Neoplasms: PA, pathology
Prostatic Neoplasms: TH, therapy
Thymidine Kinase: TU, therapeutic use
Tumor Cells, Cultured
RN 104982-03-8 (Osteocalcin); 59277-89-3 (Acyclovir)
CN 0 (Androgens); 0 (Prodrugs); EC 2.7.1.21 (Thymidine Kinase); EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 56 OF 78 CANCERLIT on STN
AN 97475098 CANCERLIT
DN 97475098 PubMed ID: 9334622
TI The prognostic value of pretreatment expression of androgen receptor and bcl-2 in hormonally treated prostate cancer patients.
AU Noordzij M A; Bogdanowicz J F; van Krimpen C; van der Kwast T H; van Steenbrugge G J
CS Department of Urology, Erasmus University, Rotterdam, The Netherlands.
SO JOURNAL OF UROLOGY, (1997 Nov) 158 (5) 1880-4; discussion 1884-5.
Journal code: 0376374. ISSN: 0022-5347.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Abridged Index Medicus Journals; Priority Journals
OS MEDLINE 97475098
EM 199711
ED Entered STN: 19971217
Last Updated on STN: 19971217
AB PURPOSE: We determined the prognostic value of oncoprotein bcl-2 and androgen receptor expression in pretreatment transurethral resection specimens of hormonally treated prostate cancer patients. MATERIALS AND METHODS: A total of 68 pretreatment transurethral resection specimens, 30 radical prostatectomy specimens and 21 palliative transurethral resection specimens with **androgen independent** prostate cancer was stained with a monoclonal antibody against bcl-2. Androgen receptor immunohistochemistry was performed on pretreatment transurethral resection specimens only. Results were scored semiquantitatively and were correlated with tumor stage and grade and with the occurrence of clinical progression or tumor related death. RESULTS: Bcl-2 expression by adenocarcinoma cells was found in 32, 17 and 24% of pretreatment transurethral resection, radical prostatectomy and palliative transurethral resection specimens, respectively. The bcl-2 scores did not correlate with tumor stage or grade. Androgen receptor was expressed in 88% of pretreatment transurethral resection specimens. Androgen receptor scores were marginally related to tumor grade, but not to tumor stage. A prognostic value of bcl-2 or androgen receptor in pretreatment transurethral resection specimens was not found. When a combined bcl-2/androgen receptor score was used, this parameter was an independent prognostic marker to predict clinical progression with Gleason grade and stage classification. Gleason grade was the only independent prognostic marker to predict tumor related death. CONCLUSIONS: The expression of bcl-2 and androgen receptor in pretreatment prostate cancer specimens is not related to the prognosis of hormonally treated prostate cancer. Bcl-2 expression is not increased in endocrine therapy resistant prostate cancer. Surprisingly, a combined bcl-2/androgen receptor score acts as an independent prognosticator for clinical progression.
CT Check Tags: Human; Male

Aged
Aged, 80 and over
Androgen Antagonists: TU, therapeutic use
Disease Progression
Disease-Free Survival
Flutamide: TU, therapeutic use
Follow-Up Studies
Gonadotropins: AI, antagonists & inhibitors
Middle Age
Multivariate Analysis
Neoplasm Staging
Orchiectomy
Prognosis
Proportional Hazards Models
Prostatectomy
***Prostatic Neoplasms: ME, metabolism**
Prostatic Neoplasms: PA, pathology
Prostatic Neoplasms: TH, therapy
*Proto-Oncogene Proteins c-bcl-2: BI, biosynthesis
*Receptors, Androgen: BI, biosynthesis
Retrospective Studies
RN 13311-84-7 (Flutamide)
CN 0 (Androgen Antagonists); 0 (Gonadotropins); 0 (Proto-Oncogene Proteins c-bcl-2); 0 (Receptors, Androgen)

L19 ANSWER 57 OF 78 CANCERLIT on STN
AN 97434302 CANCERLIT
DN 97434302 PubMed ID: 9288188
TI Target to apoptosis: a hopeful weapon for prostate cancer.
AU Tang D G; Porter A T
CS Department of Radiation Oncology, Wayne State University, Detroit, Michigan 48202, USA.. dtang@cms.cc.wayne.edu
SO PROSTATE, (1997 Sep 1) 32 (4) 284-93. Ref: 115
Journal code: 8101368. ISSN: 0270-4137.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, ACADEMIC)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 97434302
EM 199709
ED Entered STN: 19971105
Last Updated on STN: 19971105
AB BACKGROUND: Prostate cancer is the most commonly diagnosed neoplasm and the second leading cause of male death in this country. Multiple genetic and epigenetic factors have been implicated in the oncogenesis and progression of prostate cancer. However, the molecular mechanisms underlying the disease remain largely unknown. The major difficulty in the clinical management of prostate cancer stems from the reality that reliable and accurate diagnostic/prognostic biomarkers are not available and that effective treatment regimens for hormone-resistant prostate cancers are yet to be developed. METHODS: The present review, through extensive literature research, summarizes the most recently accumulated experimental and clinical data on the relationship between apoptosis and prostate cancer. We analyze the possibility of inducing prostate cancer cell apoptosis by: 1) androgen ablation by castration or biochemical antagonists: 2) chemotherapeutic drugs or natural/synthetic chemicals; 3) manipulation of apoptosis-related oncoproteins; and 4) modulation of

intracellular signal transducers. RESULTS: 1) Prostate cancer, like most other solid tumors, represents a very heterogeneous entity. Most prostate cancers, at the time of clinical diagnosis, present themselves as mixtures of androgen-dependent and **androgen-independent** cells.
2) Most prostate cancers respond initially to androgen ablation since the population of androgen-dependent cells undergoes rapid apoptosis upon androgen withdrawal. However, androgen ablation rarely cures patients, most of whom will experience recurrence due to takeover of the tumor mass by **androgen-independent** tumor cells as well as the emergence of apoptosis-resistant clones as a result of further genetic alterations such as bcl-2 amplification. 3) On the other hand, although **androgen-independent** prostate cancer cells do not undergo apoptosis upon androgen blocking, they do maintain the appropriate molecular machinery of apoptosis. Therefore, certain conventional chemotherapy drugs can eliminate **androgen-independent** cancer cells by inducing apoptosis. 4) However, most drugs used in chemotherapy induce apoptosis or mediate cytotoxicity only in proliferating cancer cells. Human prostate cancer cells demonstrate very slow growth kinetics. Thus, novel chemical/natural products need be identified to eradicate those nonproliferating cancer cells. In this regard, the angiogenesis inhibitor, linomide, and a plant extract, beta-lapachone, demonstrate very promising apoptosis-inducing effects on prostate cancer cells in a proliferation-independent manner. 5) An alternative way to modulate the apoptotic response is by interfering with the expression levels of essential regulatory molecule of apoptosis. Bcl-2 and p53 represent two prime targets for such manipulations. 6) Finally, modulation of signal transduction pathways (e.g., intracellular Ca2+ levels, PKC activity) involved in apoptosis may also induce and/or enhance the apoptotic response of prostate cancer cells. CONCLUSIONS: Modulation of apoptotic response represents a novel mechanism-based approach which may help identify novel drugs and/or develop new therapeutic regimens for the treatment of prostate cancers.

CT Check Tags: Animal; Human; Male
Androgens: PH, physiology
Antineoplastic Agents: TU, therapeutic use
*Apoptosis
Cell Division
Cell Survival
Prostatic Neoplasms: DT, drug therapy
***Prostatic Neoplasms: PA, pathology**
***Prostatic Neoplasms: TH, therapy**
Proto-Oncogene Proteins c-bcl-2: BI, biosynthesis

CN 0 (Androgens); 0 (Antineoplastic Agents); 0 (Proto-Oncogene Proteins c-bcl-2)

L19 ANSWER 58 OF 78 CANCERLIT on STN
AN 97358274 CANCERLIT
DN 97358274 PubMed ID: 9215394
TI Effect of active immunization against luteinizing hormone-releasing hormone on the androgen-sensitive Dunning R3327-PAP and **androgen-independent** Dunning R3327-AT2.1 prostate cancer sublines.
AU Fuerst J; Fiebiger E; Jungwirth A; Mack D; Talwar P G; Frick J; Rovan E
CS Department of Zoology, University of Salzburg, Austria.
SO PROSTATE, (1997 Jul 1) 32 (2) 77-84.
Journal code: 8101368. ISSN: 0270-4137.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals

OS MEDLINE 97358274
EM 199708
ED Entered STN: 19970909
Last Updated on STN: 19970909
AB BACKGROUND: The objective of this study was to determine the effect of active immunization against LHRH on the growth characteristics and histology of subcutaneously implanted tumors of the androgen-sensitive Dunning R3327-PAP and **androgen-independent** R3327-AT2.1 rat prostate adenocarcinoma sublines. RESULTS: We herein demonstrate that 1) active immunization with an LHRH-diphtheria toxoid-conjugate (LHRH-DT) leads to the downregulation of gonadotropins and testosterone and consequently the atrophy of testosterone-dependent organs such as the testes, prostate, and androgen-sensitive Dunning R3327-PAP tumors, 2) growth inhibition of Dunning R3327-PAP tumors is caused by suppression of cell division rather than by an increase in cell death and is associated with an increase of the tumor stroma content, and 3) volume increase of the **androgen-independent** Dunning R3327-AT2.1 tumor is slightly but significantly reduced, indicating a local stimulatory LHRH loop within this tumor cell line.
CT Check Tags: Animal; Male; Support, Non-U.S. Gov't
Analysis of Variance
*Cancer Vaccines
Cell Division
Cell Line
Clone Cells
Diphtheria Toxin
Follicle Stimulating Hormone: BL, blood
*Gonadorelin: IM, immunology
*Immunotherapy
Prostate: PA, pathology
Prostatic Neoplasms: BL, blood
Prostatic Neoplasms: IM, immunology
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**
Rats
Rats, Inbred F344
Testis: PA, pathology
Testosterone: BL, blood
*Testosterone: PH, physiology
*Vaccines, Synthetic
RN 33515-09-2 (Gonadorelin); 57-85-2 (Testosterone); 9002-68-0 (Follicle Stimulating Hormone)
CN 0 (Cancer Vaccines); 0 (Diphtheria Toxin); 0 (Vaccines, Synthetic)

L19 ANSWER 59 OF 78 CANCERLIT on STN
AN 97318355 CANCERLIT
DN 97318355 PubMed ID: 9175283
TI Maximal androgen blockade versus total androgen suppression.
AU Dumez H; Van Poppel H; Baert L; Paridaens R
CS Dept. of Oncology and Urology, University Hospitals KULeuven.
SO ACTA UROLOGICA BELGICA, (1997 Mar) 65 (1) 49-54.
Journal code: 0377045. ISSN: 0001-7183.
CY Belgium
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 97318355
EM 199708
ED Entered STN: 19970909

Last Updated on STN: 19970909
AB As long as advanced prostate cancer remains androgen-dependent, it can be treated by castration in combination with anti-androgens. When despite maximal androgen blockade (MAB), progression occurs, the anti-androgen withdrawal can result in partial remission. Otherwise corticosteroids can be used in low doses in order to suppress the androgens originating from the adrenal gland: total androgen suppression (TAS). The minimal side effects and the low cost price of this treatment are important advantages, given the fact that only few efficient cytostatic agents are actually available for hormone-escaped prostate cancer. About 30% of the patients with advanced prostate cancer that became **androgen independent** will show a secondary remission under low doses hydrocortisone or prednisone.
CT Check Tags: Case Report; Human; Male
Adenocarcinoma: DT, drug therapy
Adenocarcinoma: ME, metabolism
*Adenocarcinoma: TH, therapy
*Androgen Antagonists: TU, therapeutic use
Androgens: BI, biosynthesis
Combined Modality Therapy
Middle Age
Orchiectomy
Prostate-Specific Antigen: BL, blood
Prostatic Neoplasms: DT, drug therapy
Prostatic Neoplasms: ME, metabolism
***Prostatic Neoplasms: TH, therapy**
CN 0 (Androgen Antagonists); 0 (Androgens); EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 60 OF 78 CANCERLIT on STN
AN 97300054 CANCERLIT
DN 97300054 PubMed ID: 9155166
TI Mechanism on **androgen-independent** progression of prostate cancer.
AU Shimazaki J; Akakura K; Furuya Y; Ito H
CS Department of Urology, School of Medicine, Chiba University.
SO NIPPON RINSHO. JAPANESE JOURNAL OF CLINICAL MEDICINE, (1997 May) 55 (5) 1143-8. Ref: 23
Journal code: 0420546. ISSN: 0047-1852.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA Japanese
FS MEDLINE; Priority Journals
OS MEDLINE 97300054
EM 199707
ED Entered STN: 19970806
Last Updated on STN: 19970806
AB Eighty percent of prostate cancer with metastasis respond to androgen ablasion, showing initial androgen-sensitive growth. However, more than half of responders gradually loses dependency up to 5 years. Animal experiments reveal that loss of androgen sensitivity is attributable to complex reasons; adaptation, paracrine control by other **androgen -independent** tissues, genetic changes and mutation of androgen receptor. Most important event is explained from alteration of expression on oncogenes and suppressor genes. Counterplan of the progression was discussed.
CT Check Tags: Animal; Human; Male

*Androgen Antagonists: TU, therapeutic use
*Androgens: PH, physiology
Disease Progression
Drug Resistance, Neoplasm
English Abstract
Gene Expression Regulation, Neoplastic
Genes, Tumor Suppressor
Mutation
Orchiectomy
Prostatic Neoplasms: GE, genetics
***Prostatic Neoplasms: PA, pathology**
Prostatic Neoplasms: TH, therapy
Receptors, Androgen: GE, genetics
Tumor Cells, Cultured
CN 0 (Androgen Antagonists); 0 (Androgens); 0 (Receptors, Androgen)

L19 ANSWER 61 OF 78 CANCERLIT on STN
AN 97149783 CANCERLIT
DN 97149783 PubMed ID: 8996577
TI Highlights of abstracts on hormone-refractory prostate cancer presented at the 1996 annual meeting of the American Society of Clinical Oncology.
AU Roth B J
CS Department of Medicine, Indiana University Medical Center, Indianapolis 46202-5289, USA.
SO SEMINARS IN ONCOLOGY, (1996 Dec) 23 (6 Suppl 14) 6-7.
Journal code: 0420432. ISSN: 0093-7754.
CY United States
DT Conference; Conference Article; (CONGRESSES)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 97149783
EM 199702
ED Entered STN: 19970305
Last Updated on STN: 19970305
AB Among the more interesting studies at the 1996 annual meeting of the American Society of Clinical Oncology that related to hormone-refractory prostate cancer were several that reported on the use of cis-retinoic acid both alone and in combination with interferon-alpha. Interferon-alpha and interferon-alpha plus cis-retinoic acid have antiproliferative effects in vitro against both PC3 and D-145 prostate cancer cells in culture. BCL2 expression is increased in **androgen-independent** cells, which may block apoptosis, and retinoids induce transforming growth factor-beta and apoptosis in prostate cancer cell lines. This regimen raises many questions. For example, it is difficult to determine what prostate-specific antigen (PSA) level one should expect from cis-retinoic acid, 4HPR, or any of the other differentiating agents. Should there be an increase in PSA1 Should one expect a slower decline in PSA when giving additional agents that are in fact cytotoxic? What is the significance of a changing level of PSA after this and other types of treatment? These and other questions remain to be determined in future studies.
CT Check Tags: Human; Male
Antineoplastic Agents: TU, therapeutic use
Apoptosis
*Neoplasms, Hormone-Dependent
Neoplasms, Hormone-Dependent: ME, metabolism
Neoplasms, Hormone-Dependent: PA, pathology
Neoplasms, Hormone-Dependent: TH, therapy
Prostate-Specific Antigen: ME, metabolism
***Prostatic Neoplasms**

Prostatic Neoplasms: ME, metabolism
Prostatic Neoplasms: PA, pathology
Prostatic Neoplasms: TH, therapy
Tretinoin: TU, therapeutic use
RN 302-79-4 (Tretinoin)
CN 0 (Antineoplastic Agents); EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 62 OF 78 CANCERLIT on STN
AN 97041568 CANCERLIT
DN 97041568 PubMed ID: 8886839
TI Molecular therapy with recombinant p53 adenovirus in an **androgen -independent**, metastatic human prostate cancer model.
AU Ko S C; Gotoh A; Thalmann G N; Zhau H E; Johnston D A; Zhang W W; Kao C; Chung L W
CS Urology Research Laboratory, University of Texas M.D. Anderson Cancer Center, Houston 77030, USA.
SO HUMAN GENE THERAPY, (1996 Sep 10) 7 (14) 1683-91.
Journal code: 9008950. ISSN: 1043-0342.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 97041568
EM 199701
ED Entered STN: 19970205
Last Updated on STN: 19970509
AB The lethal phenotypes of advanced prostate cancer are **androgen independent** (AI) and metastatic to the axial skeleton. Our laboratory has developed an AI mouse model of metastatic human prostate cancer. In this communication, we report the development of tumor suppressor gene therapy in this AI and metastatic (C4-2) cancer model. By using recombinant adenovirus as a delivery vehicle, we introduced a wild-type p53 tumor suppressor gene into prostate cancer cell lines. Despite a silent mutation at codon 152 of the p53 gene, C4-2 cells express functional, but low, levels of p53 protein. However, the other prostatic cell lines, PC-3 and DU145, have a deletion mutation and two point mutations of the p53 gene, respectively. In vitro studies showed that cell growth, as measured by the thymidine incorporation assay, was inhibited in the C4-2, PC-3, and DU145 cells infected with wild-type p53 adenovirus in comparison to control viruses. Recombinant wild-type p53 adenovirus inhibited prostate tumor growth and its production of prostate-specific antigen (PSA) when injected into C4-2 tumors in nude mice. All p53-treated mice were tumor free as long as 12 weeks after cessation of the 8-week treatment regimen. Two of 8 p53-treated mice developed small tumors growing at distant sites after a prolonged period of follow-up observation. Moreover, other AI prostate cancer cells, PC-3 and DU145, treated with Ad5-CMV-p53 failed to develop into tumors in vivo. This gene therapy strategy may be used against AI prostatic cancer regardless of p53 gene mutation status.
CT Check Tags: Animal; Human; Male
*Adenoviruses, Human: GE, genetics
Androgens: PH, physiology
Cell Division
Gene Expression Regulation, Neoplastic
*Gene Therapy: MT, methods
Gene Transfer Techniques
*Genes, p53: GE, genetics
Genetic Vectors: GE, genetics
Mice

Mice, Nude
Mutation
Neoplasm Metastasis
Prostate-Specific Antigen: BL, blood
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**
Protein p53: AN, analysis
Tumor Cells, Cultured
CN 0 (Androgens); 0 (Genetic Vectors); 0 (Protein p53); EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 63 OF 78 CANCERLIT on STN
AN 96416207 CANCERLIT
DN 96416207 PubMed ID: 8819113
TI Does an inability to eradicate normal stem cells preclude the cure of some cancers?.
AU Anderson K M; Bonomi P; Harris J E
CS Department of Medicine, Rush Medical College, Chicago, IL 60612, USA.
SO MEDICAL HYPOTHESES, (1996 Jul) 47 (1) 31-4. Ref: 24
Journal code: 7505668. ISSN: 0306-9877.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 96416207
EM 199702
ED Entered STN: 19970305
Last Updated on STN: 19970509
AB Presently, identified signal transduction pathways do not alter normal stem-cell survival. With prostate cancer as a model, the argument is advanced that an inability to eradicate normal androgen-dependent prostate stem-cells precludes successful treatment of transformed, **androgen -independent** and metastatic progeny. While applying this idea to cancers of non-essential organs or to endocrine cancers seems feasible, the inutility of this approach for most other malignancies appears likely, although not certain.
CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't
Apoptosis
Biological Markers
Cell Differentiation
*Cell Transformation, Neoplastic
Evolution
Genes, Homeobox
Models, Biological
Prostaglandins: PH, physiology
*Prostate: PA, pathology
***Prostatic Neoplasms: PA, pathology**
***Prostatic Neoplasms: TH, therapy**
Signal Transduction
*Stem Cells: CY, cytology
Stem Cells: PA, pathology
Stem Cells: RE, radiation effects
Telomerase: ME, metabolism
CN 0 (Biological Markers); 0 (Prostaglandins); EC 2.7.7.- (Telomerase)

L19 ANSWER 64 OF 78 CANCERLIT on STN
AN 96369495 CANCERLIT

DN 96369495 PubMed ID: 8773501
TI Is there a role for induction androgen deprivation prior to radical prostatectomy?.
AU Watson R; Soloway M S
CS Department of Urology, University of Miami School of Medicine, Florida, USA.
SO HEMATOLOGY/ONCOLOGY CLINICS OF NORTH AMERICA, (1996 Jun) 10 (3) 627-41. Ref: 62
Journal code: 8709473. ISSN: 0889-8588.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 96369495
EM 199612
ED Entered STN: 19970108
Last Updated on STN: 19970108
AB The potential advantages of neoadjuvant androgen deprivation include decreased prostatic size, reduced vasculature, and reduced incidence of positive margins. The potential disadvantages are the side effects of hormonal medication, cost, tissue reaction, treatment "delay," and progression of **androgen-independent** clones. Many theories have been postulated to explain the observed reduction in the incidence of positive margins with neoadjuvant hormonal treatment. It is possible that the reduced prostate size and the frequently found periprostatic tissue reaction facilitate dissection, allowing better cancer clearance. It is possible, however, that the fibrosis may also increase the surgical difficulty, which critics argue may increase the risk of a positive margin. It is difficult to conceive of a research methodology that could resolve this issue. The occurrence of tumor cell death is likely a more significant explanation for the improved results. Whether tumor cells beyond the prostatic capsule are consistently affected to pathologically downstage the disease is unknown. The careful pathologic assessment in the randomized trials discussed previously suggests that pathologic downstaging is not as common as earlier reports have suggested. Difficulty in interpreting pathologic specimens after neoadjuvant treatment must be considered. At this point, neoadjuvant hormonal treatment prior to surgery would appear appropriate for those patients at high risk of having a positive surgical margin. Specifically, this includes clinical stage T2b, PSA elevation greater than 10 to 20 ng/mL, and a high Gleason score on the prostatic biopsy. Research to date suggests that neoadjuvant hormonal therapy prior to radical prostatectomy has a significant effect in reducing the incidence of positive surgical margins. The treatment is well tolerated with minimal side effects. Whether this will translate into improved disease-free survival remains to be determined. Fortunately, the randomized trials have been completed and follow-up data will be forthcoming.
CT Check Tags: Human; Male
*Androgen Antagonists: TU, therapeutic use
*Androgens: DF, deficiency
Combined Modality Therapy
*Preoperative Care: MT, methods
*Prostatectomy
Prostatic Neoplasms: SU, surgery
***Prostatic Neoplasms: TH, therapy**
*Receptors, LHRH: AG, agonists
Treatment Outcome

CN 0 (Androgen Antagonists); 0 (Androgens); 0 (Receptors, LHRH)

L19 ANSWER 65 OF 78 CANCERLIT on STN
AN 96338930 · CANCERLIT
DN 96338930 PubMed ID: 8725890
TI Optimal duration of neoadjuvant androgen withdrawal therapy before radical prostatectomy in clinically confined prostate cancer.
AU Gleave M E; Goldenberg S L; Jones E C; Bruchovsky N; Kinahan J; Sullivan L D
CS Division of Urology, University of British Columbia, Vancouver Hospital, Canada.
SO SEMINARS IN UROLOGIC ONCOLOGY, (1996 May) 14 (2 Suppl 2) 39-45; discussion 46-7. Ref: 26
Journal code: 9514993. ISSN: 1081-0943.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 96338930
EM 199610
ED Entered STN: 19961106
Last Updated on STN: 19970509
AB Experimental studies have shown that neoadjuvant androgen therapy dramatically reduces the rate of local recurrence after tumor excision. In the clinical setting, a 3-month course of neoadjuvant therapy before radical prostatectomy has been shown to significantly reduce positive margin rates, but follow-up is too short to assess the impact of such therapy on biochemical and clinical recurrence rates. A phase II study using an ultrasensitive assay showed that 8 months of neoadjuvant therapy were required before prostate-specific antigen (PSA) levels to reach their nadir in 84% of study participants. The positive margin rate in this study was substantially lower than those reported in the literature. Importantly, restaging of specimens after prostatic acid phosphatase (PAP) immunostaining did not upstage or increase positive margin rates. In addition, prolonged neoadjuvant therapy did not appear to result in progression of **androgen-independent** clones. A randomized phase III trial has been initiated to determine whether an 8-month course of neoadjuvant hormonal therapy is superior to a 3-month course in reducing positive margin rates and biochemical recurrences in patients with clinically confined prostate cancer.
CT Check Tags: Human; Male
Adult
Aged
*Androgen Antagonists: TU, therapeutic use
*Antineoplastic Agents, Hormonal: TU, therapeutic use
Chemotherapy, Adjuvant
Middle Age
Prostate-Specific Antigen: BL, blood
*Prostatectomy
Prostatic Neoplasms: BL, blood
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**
Time Factors
Treatment Outcome
CN 0 (Androgen Antagonists); 0 (Antineoplastic Agents, Hormonal); EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 66 OF 78 CANCERLIT on STN
AN 96238117 CANCERLIT
DN 96238117 PubMed ID: 8650872
TI Acid phosphatase: defining a role in **androgen-independent** prostate cancer.
AU Steineck G; Kelly W K; Mazumdar M; Vlamis V; Schwartz M; Scher H I
CS Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA.
SO UROLOGY, (1996 May) 47 (5) 719-26.
Journal code: 0366151. ISSN: 0090-4295.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 96238117
EM 199607
ED Entered STN: 19960807
Last Updated on STN: 19960807
AB OBJECTIVES. In multivariable analysis, post-therapy change in prostate-specific antigen (PSA) was shown to be the most significant factor predictive of survival in patients with **androgen-independent** prostate cancer. To refine the model, we studied the patterns of change in acid phosphatase, alkaline phosphatase, and lactate dehydrogenase after treatment. METHODS. One hundred seven patients with **androgen-independent** prostate cancer treated on seven different protocols in Memorial Sloan-Kettering Cancer Center were evaluated. For tumor-specific (acid phosphatase and PSA) and nontumor-specific (alkaline phosphatase and lactate dehydrogenase) enzymes, a minimum 50% or 80% decrease from baseline documented on three separate occasions a minimum of 6 weeks apart was required to categorize a patient as having a decline. RESULTS. Nineteen patients (18%) had either a 50% decline in acid phosphatase or PSA, of whom 13 (68%) had a decline of both markers. Six (32%) patients showed discordance between the two parameters. Declines in PSA level typically preceded declines in acid phosphatase levels. The median survival of patients showing declines in both markers exceeded that of patients showing declines in PSA alone by 1 year. Although baseline measurements of alkaline phosphatase or lactate dehydrogenase did add additional prognostic information, post-therapy changes did not. CONCLUSIONS. Post-therapy declines in PSA and acid phosphatase represent reproducible endpoints for clinical trials in **androgen-independent** disease. The requirement of a repeated and parallel decline in both markers may improve the results observed by monitoring declines in PSA alone. Monitoring the two parameters may allow the development of models that can be used as surrogate endpoints for response and survival in a disease in which reproducible measurements of response are lacking.
CT Check Tags: Human; Male; Support, Non-U.S. Gov't
*Acid Phosphatase: BL, blood
Aged
Aged, 80 and over
*Alkaline Phosphatase: BL, blood
Follow-Up Studies
*Lactate Dehydrogenase: BL, blood
Middle Age
Proportional Hazards Models
Prostate-Specific Antigen: BL, blood
***Prostatic Neoplasms: BL, blood**
Prostatic Neoplasms: MO, mortality
Prostatic Neoplasms: TH, therapy

Survival Analysis
CN EC 1.1.1.27 (Lactate Dehydrogenase); EC 3.1.3.1 (Alkaline Phosphatase); EC 3.1.3.2 (Acid Phosphatase); EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 67 OF 78 CANCERLIT on STN
AN 96211759 CANCERLIT
DN 96211759 PubMed ID: 8630226
TI Neuroendocrine differentiation and hormone-refractory prostate cancer.
AU Abrahamsson P A
CS Department of Urology, Lund University, Malmo, Sweden.
SO PROSTATE. SUPPLEMENT, (1996) 6 3-8. Ref: 26
Journal code: 9003050. ISSN: 1050-5881.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 96211759
EM 199606
ED Entered STN: 19960807
Last Updated on STN: 19960807
AB There is an intriguing link between differentiation of neuroendocrine cells and tumor progression in prostate cancer. Neuroendocrine differentiation appears to be associated with the **androgen-independent** state, for which there is currently no successful therapy. However, the role of the neuroendocrine cells is complex, both in the normal prostate and in the pathway toward malignancy. One important area of research is to investigate the hormones expressed by prostatic neuroendocrine cells and, in particular, to elucidate their significance to androgen independence. It is hoped that an understanding of the specific roles of hormones such as somatostatin, bombesin, and serotonin in prostate cancer may lead to improved therapeutic approaches.
CT Check Tags: Human; Male
Bombesin: TU, therapeutic use
Cell Differentiation
*Neurosecretory Systems: CY, cytology
Prognosis
***Prostatic Neoplasms: PA, pathology**
Prostatic Neoplasms: TH, therapy
Serotonin Antagonists: TU, therapeutic use
Somatostatin: TU, therapeutic use
RN 31362-50-2 (Bombesin); 51110-01-1 (Somatostatin)
CN 0 (Serotonin Antagonists)

L19 ANSWER 68 OF 78 CANCERLIT on STN
AN 96094543 CANCERLIT
DN 96094543 PubMed ID: 7490838
TI Biochemical and pathological effects of 8 months of neoadjuvant androgen withdrawal therapy before radical prostatectomy in patients with clinically confined prostate cancer.
CM Comment in: J Urol. 1996 Jan;155(1):226-7
AU Gleave M E; Goldenberg S L; Jones E C; Bruchovsky N; Sullivan L D
CS Department of Surgery, University of British Columbia, Vancouver Hospital and Health Sciences Centre, Canada.
SO JOURNAL OF UROLOGY, (1996 Jan) 155 (1) 213-9.
Journal code: 0376374. ISSN: 0022-5347.
CY United States
DT (CLINICAL TRIAL)

(CONTROLLED CLINICAL TRIAL)
Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Abridged Index Medicus Journals; Priority Journals
OS MEDLINE 96094543
EM 199601
ED Entered STN: 19960208
Last Updated on STN: 19960208
AB PURPOSE: A prospective, nonrandomized trial was initiated to determine the duration of neoadjuvant therapy required for prostate specific antigen (PSA) to reach its nadir, evaluate the ability of an ultrasensitive assay to measure decreases in PSA less than 0.2 microgram./l., and characterize the effects of 8 months of neoadjuvant therapy on pathological stage, positive margin rates, proliferation and tumor marker immuno-staining. MATERIALS AND METHODS: We evaluated 50 patients with clinically localized prostate cancer treated by 8 months of reversible androgen ablation before radical prostatectomy. Serum PSA and testosterone levels were measured monthly. RESULTS: Serum PSA decreased by 84% after 1 month and by a further 52% between 3 and 8 months. Using an ultrasensitive assay, serum PSA decreased to undetectable levels (less than 0.1 microgram./l.) or reached its nadir in 22% of the cases after 3 months, 42% after 5 months and 84% after 8 months. Overall, the positive margin rate was 4%. Of the cases 68% were organ-confined and 24% were specimen-confined. The positive margin rate was not increased after reevaluation with cytokeratin, PSA and prostatic acid phosphatase immuno-staining but of 4 cases initially staged as P0 on hematoxylin and eosin evaluation 2 had microscopic foci of cancer with prostatic acid phosphatase staining. Immuno-staining with the proliferation markers proliferation cell nuclear antigen and Ki-67 showed decreased staining in surgical specimens relative to pretreatment needle biopsy specimens, which suggests that outgrowth of **androgen independent** clones does not develop during prolonged neoadjuvant therapy. CONCLUSIONS: Eight months of neoadjuvant androgen withdrawal therapy results in low positive margin rates and PSA nadir levels. The initial rapid decrease in PSA results from cessation of androgen regulated PSA synthesis and apoptosis, while the ongoing slower decrease reflects decreasing tumor volume.
CT Check Tags: Human; Male; Support, Non-U.S. Gov't
*Androgen Antagonists: TU, therapeutic use
*Antineoplastic Agents: TU, therapeutic use
Chemotherapy, Adjuvant
Cyproterone Acetate: TU, therapeutic use
Diethylstilbestrol: TU, therapeutic use
Flutamide: TU, therapeutic use
Gonadorelin: AG, agonists
Middle Age
Neoplasm Staging
Prospective Studies
*Prostate: PA, pathology
*Prostate-Specific Antigen: BL, blood
*Prostatectomy
Prostatic Neoplasms: BL, blood
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**
Testosterone: BL, blood
Time Factors
Tumor Markers, Biological: AN, analysis
RN 13311-84-7 (Flutamide); 33515-09-2 (Gonadorelin); 427-51-0 (Cyproterone Acetate); 56-53-1 (Diethylstilbestrol); 57-85-2 (Testosterone)
CN 0 (Androgen Antagonists); 0 (Antineoplastic Agents); 0 (Tumor Markers,

Biological); EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 69 OF 78 CANCERLIT on STN
AN 95316856 CANCERLIT
DN 95316856 PubMed ID: 7796410
TI Application of a tumor suppressor (C-CAM1)-expressing recombinant adenovirus in **androgen-independent** human prostate cancer therapy: a preclinical study.
AU Kleinerman D I; Zhang W W; Lin S H; Nguyen T V; von Eschenbach A C; Hsieh J T
CS Department of Urology, University of Texas M. D., Anderson Cancer Center, Houston 77030, USA.
NC CA 16672 (NCI)
CA 59939 (NCI)
GM 43189 (NIGMS)
SO CANCER RESEARCH, (1995 Jul 1) 55 (13) 2831-6.
Journal code: 2984705R. ISSN: 0008-5472.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 95316856
EM 199508
ED Entered STN: 19950906
Last Updated on STN: 19970509
AB Recently, we demonstrated that an androgen-regulated cell adhesion molecule, C-CAM, acts as a tumor suppressor in prostate cancer development. In this study, we further explored the possibility of applying C-CAM as a potential agent for developing prostate cancer gene therapy using an adenoviral delivery system. We found that prostate cancer cells, in general, were sensitive to adenoviral infection. In vitro characterization indicated that C-CAM1 protein was detected only in C-CAM1 adenovirus-infected cells but not in antisense control virus-infected cells, and the levels of expression showed dose dependency. Because of the stability of the protein, C-CAM expression in viral-infected cells appeared to be a long-lasting event, indicating that C-CAM may be superior to many other known tumor suppressors that have a short protein half-life. Most importantly, the delivery of a single dose of C-CAM adenovirus was able to repress the growth of PC-3-induced tumors in nude mice for at least 3 weeks. Taken together, these data indicate that C-CAM is a potential candidate for human prostate cancer therapy.
CT Check Tags: Animal; Human; In Vitro; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
*Adenosinetriphosphatase: AD, administration & dosage
Adenoviridae: GE, genetics
Base Sequence
*Cell Adhesion Molecules: AD, administration & dosage
DNA Primers: CH, chemistry
Gene Therapy
Gene Transfer Techniques
*Genes, Tumor Suppressor
Mice
Mice, Nude
Molecular Sequence Data
Neoplasm Transplantation
***Prostatic Neoplasms: TH, therapy**
Recombinant Proteins
Tumor Cells, Cultured
CN 0 (Cell Adhesion Molecules); 0 (DNA Primers); 0 (Recombinant Proteins); 0

(cell-CAM 105); EC 3.6.1.3 (Adenosinetriphosphatase)

L19 ANSWER 70 OF 78 CANCERLIT on STN
AN 95252897 CANCERLIT
DN 95252897 PubMed ID: 7735002
TI Androgen action: molecular mechanism and medical application.
AU Liao S
CS Ben May Institute, Department of Biochemistry and Molecular Biology, University of Chicago, Illinois 60637, USA.
NC CA 59073 (NCI)
DK 37694 (NIDDK)
DK41670 (NIDDK)
SO JOURNAL OF THE FORMOSAN MEDICAL ASSOCIATION, (1994 Sep) 93 (9) 741-51. Ref: 85
Journal code: 9214933. ISSN: 0929-6646.
CY TAIWAN: Taiwan, Province of China
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW LITERATURE)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 95252897
EM 199506
ED Entered STN: 19950707
Last Updated on STN: 19950707
AB Androgen action in many organs, such as prostate and skin, is dependent on the conversion of testosterone by 5 alpha-reductase to 5 alpha-dihydrotestosterone. 5 alpha-Dihydrotestosterone then binds to the androgen receptor to regulate specific gene expression. Inhibitors of 5 alpha-reductase are useful for the selective treatment of prostatic cancer, benign prostate hyperplasia, acne, baldness and female hirsutism, without affecting spermatogenesis, sexual behavior and smooth muscle growth, that do not require the conversion of testosterone to 5 alpha-dihydrotestosterone. Certain unsaturated fatty acids, such as gamma-linolenic acid, are potent 5 alpha-reductase inhibitors, suggesting a linkage between unsaturated fatty acids and androgen action. Mutations in androgen receptor genes are responsible for many cases of androgen-insensitivity. In some prostate cancer cells, some antiandrogens may act like androgens in stimulating the proliferation of the cancer cells because these antiandrogens can bind to a mutated androgen receptor and transactivate target genes. Prostate cancers are usually androgen-dependent initially but can lose dependency and responsiveness. Tumor cells which are resistant to endocrine therapy ultimately proliferate. **Androgen-independent** or androgen-repressive cells can arise from androgen-sensitive prostate cancer cells by changes in specific gene expression over time in a clonal isolate. This change in androgen responsiveness was accompanied by a change in androgen receptor expression and transcriptional activity as well as expression of some oncogenes.
CT Check Tags: Human; Male; Support, U.S. Gov't, P.H.S.
Androgen Antagonists: ME, metabolism
Androgens: CH, chemistry
Androgens: GE, genetics
Androgens: ME, metabolism
*Androgens: PH, physiology
Base Sequence
Molecular Sequence Data
Prostatic Neoplasms: GE, genetics
Prostatic Neoplasms: ME, metabolism

Prostatic Neoplasms: TH, therapy
Receptors, Androgen: CH, chemistry
Receptors, Androgen: GE, genetics
Receptors, Androgen: PH, physiology
Skin Diseases: GE, genetics
Skin Diseases: ME, metabolism
Testosterone 5-alpha-Reductase: AI, antagonists & inhibitors
Testosterone 5-alpha-Reductase: GE, genetics
Testosterone 5-alpha-Reductase: ME, metabolism
Testosterone 5-alpha-Reductase: PH, physiology
CN 0 (Androgen Antagonists); 0 (Androgens); 0 (Receptors, Androgen); EC 1.3.99.5 (Testosterone 5-alpha-Reductase)

L19 ANSWER 71 OF 78 CANCERLIT on STN
AN 95230785 CANCERLIT
DN 95230785 PubMed ID: 7536271
TI The results of a phase II randomized trial comparing 5-fluorouracil and 5-fluorouracil plus alpha-interferon: observations on the design of clinical trials for **androgen-independent** prostate cancer.
CM Comment in: J Urol. 1995 May;153(5):1592-3
AU Daliani D D; Eisenberg P D; Weems J; Lord R; Fueger R; Logothetis C J
CS Department of Genitourinary Medical Oncology, University of Texas M.D. Anderson Cancer Center, Houston 77030, USA.
NC N01-CM-07310 (NCI)
SO JOURNAL OF UROLOGY, (1995 May) 153 (5) 1587-91.
Journal code: 0376374. ISSN: 0022-5347.
CY United States
DT (CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE II)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LA English
FS MEDLINE; Abridged Index Medicus Journals; Priority Journals
OS MEDLINE 95230785
EM 199505
ED Entered STN: 19950608
Last Updated on STN: 19960517
AB The therapeutic benefit of chemotherapy in **androgen independent** prostate cancer is limited. 5-Fluorouracil has been reported to have modest antitumor activity in **androgen independent** prostate cancer. Although alpha-interferon is inactive as a single agent in prostate cancer, preclinical data indicate that it increases the in vitro cytotoxicity of 5-fluorouracil against a variety of malignant cells. We evaluated the relative antitumor activity and tolerance of 5-fluorouracil versus 5-fluorouracil plus alpha-interferon in 50 patients with histologically confirmed metastatic adenocarcinoma of the prostate. These patients had progressive disease in the presence of castrate levels of testosterone. A prospective randomized phase II open labeled trial was performed because of the difficulty in measuring responses in patients with metastatic prostate cancer. Of 23 patients treated with 5-fluorouracil alone and 28 treated with 5-fluorouracil plus alpha-interferon 17 and 23, respectively, were evaluable for response and toxicity, and 5 and 5, respectively, were evaluable for toxicity only. Only 2 of 17 (11.7%) and 4 of 23 (17%) patients, respectively, showed a greater than 50% decrease in serum prostate specific antigen (no significant difference). There was no difference in duration of response or duration of survival between the 2 groups (mean duration of response 8.64 and 6.17 weeks, respectively, and mean duration of survival 33.70 and

38.65 weeks, respectively). Both regimens caused significant morbidity (mucositis and neurotoxicity) and 3 treatment related deaths at the high 5-fluorouracil doses. 5-Fluorouracil alone and with alpha-interferon at the doses used have minimal antitumor activity against **androgen independent** prostate cancer and, therefore, should not be tested further in these patients. **Androgen independent** prostate cancer selected using our criteria is a rapidly progressive disease, and these patients are an ideal target population for phase II studies.

CT Check Tags: Comparative Study; Human; Male; Support, U.S. Gov't, P.H.S.
Adenocarcinoma: MO, mortality
Adenocarcinoma: SC, secondary
*Adenocarcinoma: TH, therapy
Aged
Disease Progression
Fluorouracil: AD, administration & dosage
Fluorouracil: AE, adverse effects
*Fluorouracil: TU, therapeutic use
Interferon-alpha: AD, administration & dosage
Interferon-alpha: AE, adverse effects
*Interferon-alpha: TU, therapeutic use
Prospective Studies
Prostate-Specific Antigen: BL, blood
Prostatic Neoplasms: MO, mortality
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**
Research Design
Survival Rate
Time Factors

RN 51-21-8 (Fluorouracil)

CN 0 (Interferon-alpha); EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 72 OF 78 CANCERLIT on STN

AN 95187206 CANCERLIT

DN 95187206 PubMed ID: 7881465

TI Apoptosis: therapeutic significance in the treatment of androgen-dependent and **androgen-independent** prostate cancer.

AU Kyprianou N

CS Department of Surgery, University of Maryland Medical Center, Baltimore 21201.

SO WORLD JOURNAL OF UROLOGY, (1994) 12 (6) 299-303. Ref: 48
Journal code: 8307716. ISSN: 0724-4983.

CY GERMANY: Germany, Federal Republic of

DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LA English

FS MEDLINE; Priority Journals

OS MEDLINE 95187206

EM 199504

ED Entered STN: 19950509 .
Last Updated on STN: 19970509

AB To improve survival in men with metastatic prostatic cancer, a therapeutic modality that can effectively eliminate **androgen-independent** cancer cells is needed desperately. Combination of such an effective modality with androgen ablation could affect all of the heterogeneous populations within prostate tumors of individual patients, thus optimizing the chances of complete cure. Such a therapeutic approach will probably require two types of agents, one with antiproliferative

activity affecting the small number of dividing **androgen-independent** cells and one with the capacity to increase the rate of cell death among the non-proliferating **androgen-independent** prostatic cancer cells present, i.e. the majority. Androgen-responsive human prostate cancer cells are able to undergo programmed cell death after androgen ablation (even if the cells are not in the proliferative cell cycle). **Androgen-independent** human prostate cancer cells, however, do not activate this apoptotic pathway of cell death in response to androgen ablation. In contrast, **androgen-independent** human prostate cancer cells can be induced to undergo apoptosis following such alternative treatment modalities as: (a) non-androgen ablative cytotoxic drugs, such as fluorinated pyrimidines, which result in the "thymine-less state", and (b) ionizing irradiation. The apoptotic effect induced by radiation can be significantly potentiated by post-irradiation treatment of the cells with suramin. In contrast, this radiation induced apoptosis can be substantially inhibited by pretreatment of cells with suramin, probably through suramin's ability to arrest proliferating cells in the GO/G1 phase of the cell cycle. These results suggest that treatment of prostate cancer patients with suramin prior to irradiation is likely to inhibit radiation palliation.(ABSTRACT TRUNCATED AT 250 WORDS)

CT Check Tags: Animal; Human; Male
*Androgens: PH, physiology
Antineoplastic Agents: TU, therapeutic use
*Apoptosis
Combined Modality Therapy
Prostate: PA, pathology
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**
*Suramin: TU, therapeutic use
Tumor Cells, Cultured

RN 145-63-1 (Suramin)
CN 0 (Androgens); 0 (Antineoplastic Agents)

L19 ANSWER 73 OF 78 CANCERLIT on STN
AN 93264463 CANCERLIT
DN 93264463 PubMed ID: 8494915
TI Incorporating tumor biology into therapy for prostate cancer.
AU Bromberg J; Scher H I
CS Department of Medicine, Memorial Sloan-Kettering Cancer Center, New York, NY 10021.
NC CA-05826 (NCI)
CM-57732 (NCI)
SO CURRENT OPINION IN ONCOLOGY, (1993 May) 5 (3) 546-58. Ref: 88
Journal code: 9007265. ISSN: 1040-8746.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 93264463
EM 199306
ED Entered STN: 19941107
Last Updated on STN: 19941107
AB Prostate cancer remains the most common and the second leading cause of cancer death in men. Despite the frequency of the disease, controversies in management continue for all stages. For patients with localized tumors, deciding whether any treatment is indicated and, if so, selecting the

appropriate modalities for an individual patient are at issue. For more advanced local tumors, although definitive data showing a survival benefit are lacking, several groups have been using androgen deprivation prior to surgery or radiation therapy in the hopes of improving local control rates. For patients with established metastases, the timing of androgen ablation is still debated, as is the optimal way to integrate treatments aimed at the **androgen-independent** cell population--the ultimate cause of death from prostatic cancer. In addition, several groups are focusing on methods to try to predict the natural history of the disease in an individual patient, while reserving the final recommendation on treatment based on the biologic behavior in that individual.

CT Check Tags: Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Prostatic Neoplasms: GE, genetics
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**

GEN bcl-2; p53; ras

L19 ANSWER 74 OF 78 CANCERLIT on STN
AN 93046217 CANCERLIT
DN 93046217 PubMed ID: 1841755
TI Programmed cell death as a new target for prostatic cancer therapy.
AU Kyprianou N; Martikainen P; Davis L; English H F; Isaacs J T
CS Johns Hopkins Oncology Center, Baltimore, Maryland 21205.
SO CANCER SURVEYS, (1991) 11 265-77. Ref: 68
Journal code: 8218015. ISSN: 0261-2429.
CY United States
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 93046217
EM 199212
ED Entered STN: 19941107
Last Updated on STN: 19941107
AB To increase survival of men with metastatic prostatic cancer, a modality that can effectively eliminate **androgen independent** cancer cells is desperately needed. By combining such an effective modality with androgen ablation, all of the heterogeneous populations of tumour cells within a prostatic cancer patient can be affected, thus optimizing the chances of cure. Unfortunately, such effective therapy for the **androgen independent** prostatic cancer cell is not yet available. This therapy will probably require two types of agents, one having antiproliferative activity affecting the small number of dividing **androgen independent** cells, and the other able to increase the low rate of cell death among the majority of non-proliferating (ie interphase) **androgen independent** prostatic cancer cells present. Androgen dependent prostatic epithelial cells can be made to undergo programmed death by means of androgen ablation, even if the cells are not in the proliferative cell cycle. **Androgen independent** prostatic cancer cells retain the major portion of this programmed cell death pathway, only there is a defect in the pathway such that it is no longer activated by androgen ablation. If the intracellular free Ca2+ is sustained at an elevated level for a sufficient time, **androgen independent** cells can be induced to undergo programmed death. The long term goal is therefore to develop some type of non-androgen ablative method that can be used in vivo to induce a sustained elevation in Ca2+ in **androgen**

independent prostatic cancer cells. To accomplish this task, a more complete understanding of the biochemical pathways involved in programmed cell death is urgently needed. At present, studies are focusing on the mechanism involved in the Ca2+ elevation in the normal and malignant androgen dependent cell induced following androgen ablation and the role of the TRPM-2 protein in this process.

CT Check Tags: Animal; Human; Male
Adenocarcinoma: SU, surgery
*Adenocarcinoma: TH, therapy
Androgens: PH, physiology
Calcium: PH, physiology
Castration
Cell Death: PH, physiology
Prostatic Neoplasms: SU, surgery
***Prostatic Neoplasms: TH, therapy**
Rats

RN 7440-70-2 (Calcium)
CN 0 (Androgens)

L19 ANSWER 75 OF 78 CANCERLIT on STN
AN 92279647 CANCERLIT
DN 92279647 PubMed ID: 1375772
TI [Prostate carcinoma--a current review].
Das Prostatakarzinom--eine aktuelle Ubersicht.
AU Schmid H P
CS Urologische Universitatsklinik Kantonsspital, Basel.
SO SCHWEIZERISCHE RUNDSCHAU FUR MEDIZIN PRAXIS, (1992 May 12) 81 (20) 647-53.
Ref: 70
Journal code: 8403202. ISSN: 1013-2058.
CY Switzerland
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LA German
FS MEDLINE; Priority Journals
OS MEDLINE 92279647
EM 199207
ED Entered STN: 19941107
Last Updated on STN: 19960517
AB Carcinoma of the prostate is the most commonly diagnosed cancer in men. The natural history and the biological aggressiveness are primarily determined by tumor volume. At the time of diagnosis, only one third of all tumors are pathologically confined to the prostate and eligible for curative therapy. Early detection by the general practitioner with prostate-specific antigen and digital rectal examination should be the primary goal. Currently, diagnosis is best established by transrectal ultrasound-guided biopsies. For the treatment of localized prostate cancer, men who undergo radical retropubic prostatectomy have been shown to have superior long-term results when compared to those who have received radiation therapy. With an improved understanding of the prostatic anatomy and nerve-sparing surgical techniques, morbidity from impotence and incontinence are minimal. In advanced carcinoma, 70 to 80% of men initially respond well to androgen withdrawal. Unfortunately, **androgen-independent** cells will continue to multiply, leading to tumor progression and death. Until effective chemotherapeutic agents are developed, we can only achieve palliation in advanced disease.
CT Check Tags: Human; Male
Antigens, Neoplasm: IP, isolation & purification
Diagnostic Imaging

English Abstract
Neoplasm Staging
Prostate: IM, immunology
Prostate-Specific Antigen
Prostatectomy
*Prostatic Neoplasms: DI, diagnosis
Prostatic Neoplasms: PA, pathology
Prostatic Neoplasms: TH, therapy
Radiotherapy: MT, methods
Tumor Markers, Biological: IP, isolation & purification
CN 0 (Antigens, Neoplasm); 0 (Tumor Markers, Biological); EC 3.4.21.77 (Prostate-Specific Antigen)

L19 ANSWER 76 OF 78 CANCERLIT on STN
AN 88268126 CANCERLIT
DN 88268126 PubMed ID: 3389834
TI Prostatic carcinoma. I: Androgen dependency of prostatic carcinoma.
AU Shimazaki J; Fuse H; Akimoto S; Sumiya H; Akakura K; Ichikawa T
CS Dept. of Urology, School of Medicine, Chiba University.
SO GAN TO KAGAKU RYOHO [JAPANESE JOURNAL OF CANCER AND CHEMOTHERAPY], (1988 Apr) 15 (4 Pt 2-1) 909-16.
Journal code: 7810034. ISSN: 0385-0684.
CY Japan
DT Journal; Article; (JOURNAL ARTICLE)
LA Japanese
FS MEDLINE; Priority Journals
OS MEDLINE 88268126
EM 198807
ED Entered STN: 19941107
Last Updated on STN: 19941107
AB Endocrine therapy, which consists of orchiectomy followed by administration of large doses of estrogen, then a reduced amount of estrogen, has been applied as the main treatment for stage D2 prostatic cancer. Alternatively, anti-androgen is used for elderly patients or those with cardiovascular disorders. Survival rate with endocrine therapy at 5 and 10 years was 35% and 16%, respectively. Therefore, in Japan, a better survival is shown than that reported in western countries using much smaller doses of estrogen. Most of the side effects caused by estrogen are not serious. Side effects caused by anti-androgen are few except for loss of libido. At the start of treatment, more than 80% of patients showed a response, but gradually relapse occurred and only 20% were well controlled 5 years after the start. Factors influencing the survival were pathological grade, response to endocrine therapy judged by the level of prostatic acid phosphatase 4 weeks after the start, and R1881 (methyltrienolone)-binding protein observed histochemically. The latter protein was also correlated with the grade and response to endocrine therapy. Relapse after endocrine therapy might be attributable to adaptation or mutation progressing to **androgen-independent** cells. Using SC 115, an androgen-dependent mouse tumor, these two types of relapse were demonstrated. Gradual progression to undifferentiated cancer was noticed between pretreatment biopsy and autopsy. Relapse in human prostatic cancer may thus be partly due to genetic change to a resistant clone.
CT Check Tags: Animal; Human; Male; Support, Non-U.S. Gov't
Androgen Antagonists: TU, therapeutic use
*Androgens: PH, physiology
English Abstract
Estrogens: TU, therapeutic use
Mice

*Neoplasms, Hormone-Dependent: PP, physiopathology
Neoplasms, Hormone-Dependent: TH, therapy
Orchiectomy
***Prostatic Neoplasms: PP, physiopathology**
Prostatic Neoplasms: TH, therapy
CN 0 (Androgen Antagonists); 0 (Androgens); 0 (Estrogens)

L19 ANSWER 77 OF 78 CANCERLIT on STN
AN 87320737 CANCERLIT
DN 87320737 PubMed ID: 3307086
TI Development of **androgen-independent** tumor cells and their implication for the treatment of prostatic cancer.
AU Isaacs J T; Kyprianou N
NC CA 15416 (NCI)
SO UROLOGICAL RESEARCH, (1987) 15 (3) 133-8. Ref: 40
Journal code: 0364311. ISSN: 0300-5623.
CY GERMANY, WEST: Germany, Federal Republic of
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 87320737
EM 198710
ED Entered STN: 19941107
Last Updated on STN: 19941107
AB Development of **androgen-independent** prostatic cancer cells from androgen-responsive cells can occur by a variety of mechanisms (e.g., environmental adaptation, multifocal origin, or genetic instability). Regardless of the mechanism of development, however, once **androgen-independent** cancer cells become present within prostatic cancer, the tumor is no longer homogeneous but is now heterogeneous. Once a prostatic cancer is heterogeneously composed of both androgen-dependent and -independent cancer cells, androgen withdrawal therapy, no matter how complete, cannot be curative. In order to produce cures of such heterogeneous prostatic cancers, hormonal therapy must be combined simultaneously with chemotherapy early in the course of the disease so that all the cancer populations (i.e., androgen-dependent and -independent) can be simultaneously affected within an individual patient.
CT Check Tags: Human; Male; Support, U.S. Gov't, P.H.S.
Androgen Antagonists: TU, therapeutic use
*Androgens: PH, physiology
Cell Differentiation
Combined Modality Therapy
Cyclophosphamide: PD, pharmacology
Cyclophosphamide: TU, therapeutic use
Flutamide: TU, therapeutic use
Gonadorelin: PD, pharmacology
Gonadorelin: TU, therapeutic use
Orchiectomy
Prostatic Neoplasms: PA, pathology
***Prostatic Neoplasms: TH, therapy**
RN 13311-84-7 (Flutamide); 33515-09-2 (Gonadorelin); 50-18-0 (Cyclophosphamide)
CN 0 (Androgen Antagonists); 0 (Androgens)

L19 ANSWER 78 OF 78 CANCERLIT on STN
AN 87215695 CANCERLIT
DN 87215695 PubMed ID: 3555779
TI Biology and therapy of prostatic cancer.

AU Schulze H; Isaacs J T
NC CA 15416 (NCI)
SO CANCER SURVEYS, (1986) 5 (3) 487-503. Ref: 80
Journal code: 8218015. ISSN: 0261-2429.
CY ENGLAND: United Kingdom
DT Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
LA English
FS MEDLINE; Priority Journals
OS MEDLINE 87215695
EM 198707
ED Entered STN: 19941107
Last Updated on STN: 19941107
AB There is no effective therapy for increasing the survival of metastatic prostatic cancer. New approaches to this major disease are urgently needed. One approach is to study the biology of prostatic carcinogenesis in order to develop a treatment that prevents the initial development of clinically manifest prostatic cancer. International epidemiological data on the incidence of prostatic cancer and the data on migrant populations make this both possible and practical. For example, it should be possible to lower the incidence of clinical prostatic cancer by more than ten-fold among men in the United States. An alternative approach is to study the tumour biology of prostatic cancer to identify better methods for treating established clinical prostatic cancer. Such studies have already demonstrated that individual prostatic cancers are composed of clones of cancer cells that are phenotypically heterogeneous even before therapy is initiated. Because of this tumour cell heterogeneity, future studies should be directed towards combining androgen ablation plus chemotherapy and/or radiation early in the disease in order to affect both the androgen-dependent and the **androgen-independent** cancer cells present in individual prostatic cancers.
CT Check Tags: Human; Male; Support, Non-U.S. Gov't; Support, U.S. Gov't, P.H.S.
Androgen Antagonists: TU, therapeutic use
Combined Modality Therapy
Drug Resistance
Epidemiologic Methods
Prostatic Neoplasms: GE, genetics
Prostatic Neoplasms: PP, physiopathology
Prostatic Neoplasms: PC, prevention & control
***Prostatic Neoplasms: TH, therapy**
CN 0 (Androgen Antagonists)